Assessment of Coronary Artery Disease by Computed Tomography

Will Roberts

Thesis submitted for the degree of Doctor of Medicine

Barts and The London
School of Medicine and Dentistry
Queen Mary University of London

Abstract

BACKGROUND

Computed Tomography Coronary Angiography (CTCA) is a technique for imaging coronary arteries with increasing indications in clinical cardiology.

AIMS

1.Develop a heart rate (HR) lowering regime for CTCA and to measure its association with image quality.

2.Examine the diagnostic accuracy of 64 slice CTCA (CTCA64) in patients with known coronary artery disease (CAD).

3.Examine the diagnostic accuracy of CTCA64 for assessment of stent restenosis

4.Demonstrate utility of CTCA as an endpoint in assessment of novel diagnostic biomarkers of CAD.

METHODS

I developed a HR reducing strategy using metoprolol and assessed its effectiveness for improving CTCA64 image quality.

The diagnostic value of CTCA in patients with suspected angina was evaluated by comparison with invasive coronary angiography.

The diagnostic value of CTCA for quantifying stent restenosis was evaluated by comparison with intravascular ultrasound.

The utility of CTCA for evaluating the diagnostic value of B-type natriuretic peptide (BNP) and high sensitivity cardiac troponin I (hs-TnI) was evaluated by blood sampling in patients with suspected angina who subsequently underwent CTCA.

RESULTS

1. In 121 patients undergoing CTCA, 75 required rate control. This was achieved (rate ≤60 bpm) in 83% using a systematic regimen of oral and IV metoprolol (n=71) or verapamil (n=4). I demonstrated a significant relation between HR reduction and graded image quality ($p<0.001$).

2. 80 patients underwent CTCA64 and invasive coronary angiography. 724 coronary arterial segments were available for analysis. The sensitivity and specificity of CTCA for

significant luminal stenosis was 83.3% (95% CI 67.1-92.5%) and 96.7% (95% CI 95.1-97.9%), respectively, but the positive predictive value was only 63.5% (95% CI 50.4-75.3%).

3. 80 patients with 125 stented segments underwent CTCA64 and invasive coronary angiography. Additional intravascular ultrasound (IVUS) examination of stented segments was performed in 48 patients. Using IVUS as the gold-standard for stent restenosis, CTCA and invasive coronary angiography had comparable diagnostic specificities for binary stent restenosis: 82.7% (95% confidence intervals 69.7-91.84%) and 78.9% (95% confidence intervals 65.3-88.9%), respectively. Sensitivities were lower, particularly the sensitivity of CTCA which was only 11.8% (95% confidence intervals 1.5-36.4%) compared with 58.8% (95% confidence intervals 32.9-81.6%) for invasive coronary angiography.

4. In 93 patients with suspected angina CTCA64 provided a useful endpoint for assessing the diagnostic value of novel circulating biomarkers. BNP levels were higher in the 13 patients shown to have significant (≥50% stenosis) coronary artery disease compared with patients who had unobstructed coronary arteries (18.08pg/ml (IQR 22) vs 9.14pg/ml (IQR 12.62), p=0.024) and increased significantly with exercise, particularly in the group with anatomic coronary artery disease (2.73 ± 5.69 pg/ml vs 1.27±3.29 pg/ml, p=0.16). Conversely I found no association between hs-TnI and the presence of CAD.

CONCLUSION

Image quality of CTCA64 is enhanced by heart rate reduction below 60 bpm which can be achieved safely by a regimen of oral and intravenous metoprolol. Although CTCA64 is a useful non-invasive method for diagnosis of coronary artery disease, it has a low positive predictive value for identifying severe (≥50%) luminal stenosis which limits its clinical value. Its value for assessment of stent restenosis is even more limited but it finds useful application as an endpoint for diagnostic evaluation of novel biomarkers, allowing confirmation of an association between circulating BNP levels and stable coronary artery disease.

Contents

List of figures

List of Tables

Glossary of key terms and acronyms

ACS	Acute coronary syndrome: encompasses both unstable angina and Myocardial infarction
AF	Atrial fibrillation - an irregular heart rhythm
Agatston	An American cardiologist whose name has been given to the score for measuring the degree of calcification within the coronary arteries visible on CT he developed
Angioplasty	See PTCA
ANP	Atrial Natriuretic Peptide
ApoB	Apolipoprotein B
β-blocker	see Beta blocker
Beta blocker	A term for beta-adrenoreceptor antagonists - a class of drugs block the action of endogenous catecholamines on β-adrenergic receptors, part of the sympathetic nervous system.
BNP	B type Natriuretic Peptide
bpm	Beats per minute
CABG	Coronary artery bypass graft: involves opening the patients chest under general anaesthetic and bypassing the narrowed arteries with vessels from elsewhere in the same patient (e.g. leg veins, internal mammary artery)
CAD	Coronary Artery Disease
CAX	Invasive coronary angiography
CD-36	Cluster of Differentiation 36 - a membrane protein
CHD	Coronary heart disease: a spectrum of clinical disorders including stable and unstable angina and acute MI
CMR	Cardiac MRI
contrast	Intravenous contrast agent - usually iodine based used to improve visibility of structures in CT imaging

CrCL	Creatinine Clearance - a measure of renal function
CT	Computed Tomography
CTCA	Computed Tomography Coronary Angiography
CTCA64	CTCA utilising a scanner with 64 detectors
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
diastasis	The middle stage of diastole during the cardiac cycle when the heart is least mobile
diastole	The part of the cardiac cycle during which ventricular relaxation occurs
DSE	Dobutamine Stress Echo
EBCT	Electron Beam CT
ECG	Electrocardiogram. A non-invasive investigation to test heart function measuring electrical currents of the heart
ETT	Exercise Tolerance Test (Exercise electrocardiography) -Non-invasive investigation to test heart function measuring electrical currents of the heart while exercising on a treadmill
FDA	United States of America Food and Drug Administration
FRISC	A study investigating the management of acute coronary syndromes entitled 'Fragmin and Fast Revascularization During Instability in Coronary Artery Disease'
GUSTO-IV	A study investigating the role of abciximab in acute coronary syndromes
HbA1C	Glycated hemoglobin - a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time.
HR	Heart Rate
hs-TnI	Cardiac Troponin I measured using a high sensitvity assay
HU	Hounsfield Units

If Channel	Cardiac pacemaker channel
iv	Intravenous
IVUS	Intravascular Ultrasound
kernel	A term for a reconstruction algorithm used to convert raw CT data into images
LDL	Low Density Lipoprotein
LV	Left Ventricle or Left Ventricular
mass concentration	The mass of a constituent substance divided by the volume of the mixture
MDCT	Multidetector CT
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
MIP	Maximum Intensity Projection
MPR	Multiplanar Reformat
MRI	Magnetic Resonance Imaging
mRNA	messenger RNA - molecule of RNA that encodes a 'blueprint' for a protein
MSCT	Multi Slice CT (also termed MDCT)
NICE	National Institute for Health and Clinical Excellence
NT-proBNP	The inactive N-terminal fragment of the prohormone proBNP which is formed when proBNP is cleaved.
PCI	Percutaneous Coronary Intervention (see PTCA)
PTCA	Percutaneous transluminal coronary angioplasty: a local anaesthetic procedure in which a balloon is inserted and inflated to dilate the narrowed coronary artery. Re-stenosis (re-narrowing) of this artery is a problem, hence stents are increasingly deployed. Percutaneous coronary intervention (PCI) is the generic term for PTCA with or without stent

RACPC	Rapid Access Chest Pain Clinic
restenosis	Development of narrowing within a previously treated (stented) coronary artery
r-wave	Part of the electrocardiographic trace corresponding to the electrical onset of systole
scintillator	A material which exhibits luminescence when excited by ionizing radiation
SMC	Smooth Muscle Cell
SPC	Summary of Product Characteristics
ST	Refers to the part of the electrocardiogram that characteristically changes during acute myocardial infarction
Stent	A metal tube inserted across the narrowed coronary artery to hold it open, can be drug-eluting (coated with drugs inhibiting intimal proliferation)
systole	The part of the cardiac cycle during which ventricular contraction occurs
TLR-2	Toll-like receptor 2 - a membrane protein also termed CD282 (cluster of differentiation 282)

Dedication

This work is dedicated to my parents who gave everything they had for me and my brothers to have the best opportunities in life.

Acknowledgments

So many people have helped me on the journey to the completion of this thesis and I am grateful to all of them.

Many thanks go to Professor Adam Timmis, and Dr Martin Carrier for their help and support. Many thanks also go to Dr Ben Timmis and Dr Andrew Wright for their support in setting up the CTCA service and funding and reviewing many CT scans.

Thanks to all the staff at Newham Hospital, The London Chest Hospital and The Hospital of St John and St Elizabeth all of whom gave extra time and effort to help with the studies and work over the last few years.

Thanks to Loreta Mostoles, research nurse for her efforts recruiting patients and Dr Sreekumar Sulfi for laying the groundwork for me.

I am grateful to Dr Cornelia Junghans for assistance with some of the statistical calculations, despite being pregnant and going through medical school at the time.

Many thanks to The Barts and London charitable trust, Siemens and The Hospital of St John and St Elizabeth for financial support and making facilities available for this work.

Declaration

The concept for this thesis was jointly formulated by me and my supervisor Prof Adam Timmis.

Chapters 1, 2 and 7 were written by me.

Chapter 3 HEART RATE AND RHYTHM DURING CT CORONARY ANGIOGRAPHY.

I developed the protocol for heart rate control used in our institution based on available evidence on pharmacology and procedures from early adopter centres. I then wrote the protocol to record the efficacy of our regime in a group of our patients. I supervised the scan of all subjects, administered the heart rate lowering medication and recorded all data. I undertook all the statistical analysis.

Chapters 4 and 5 CT FOR ASSESSING CORONARY ARTERIES, CT FOR ASSESSING CORONARY ARTERY STENTS

An outline for a study comparing CTCA and angiography for assessment of stents was written previously but this was substantially changed with the addition of intravascular ultrasound as a gold standard. I obtained ethical approval for the study and co-ordinated funding from several sources. I recruited all patients to the study, supervised all CT scans, administering medications when required. I performed all post-processing of the CT scans. I supervised performance of coronary angiography and IVUS assessments. I developed a database for documentation of all data and collected all data. I worked with a statistician to complete the binomial confidence interval tables, and all other statistical analysis was by me.

Chapter 6 CTCA AS AN ENDPOINT FOR EVALUATION OF BIOMARKERS IN STABLE CORONARY ARTERY DISEASE

I wrote the protocol for this study, obtained ethical approval and funding for a research nurse. I interviewed for and employed a research nurse and trained her to the protocol to recruit patients for the study. I supervised all CT scans for the beginning of the study, and then trained a research fellow to assist in supervision towards the end of the study. I performed all post-processing of the scans. I developed a database and collected all data. All statistical analysis was done by me.

Aims

1. Develop a heart rate lowering regime for CTCA and to measure association with image quality. (Chapter 3)

2. Examine the diagnostic accuracy of 64 slice CTCA in patients with known coronary artery disease. (Chapter 4)

3. Examine the diagnostic accuracy of 64 slice CTCA for quantifying stent restenosis. (Chapter 5)

4. Demonstrate utility of CTCA as an endpoint in assessment of novel biomarkers. (Chapter 6)

1. INTRODUCTION

In this thesis the technique of computed tomography (CT) and its role in the assessment of coronary disease and the utility of the biomarkers cardiac Troponin I (cTnI) and B-type natriuretic peptide in the setting of stable chest pain will be explored.

The technology of CT coronary angiography (CTCA) will be examined and the importance of heart rate control when acquiring images of the heart will be explored and a regime to lower patients' heart rates at the time of performing a CTCA scan will be investigated. The existing evidence on the diagnostic accuracy of CTCA in the context of native vessels and coronary arteries that have previously had stents placed will be reviewed and the application of 64 slice CTCA to a cohort with previously treated coronary disease will be explored with comparison of accuracy with published data.

The utility of CTCA as an endpoint in suspected CAD will be demonstrated with a cross-sectional assessment of the application of calcium scoring, CTCA, BNP and cTnI in addition to exercise testing and clinical assessment in the setting of patients presenting with stable angina symptoms.

This chapter first outlines the background to the atherosclerotic disease process that leads to coronary artery disease, its prevalence and impact on health. Having outlined the importance of coronary artery disease, the current methods for assessing and treating coronary artery disease will be explored before examining the technology and technique of CTCA and exploring the current evidence supporting the use of CTCA. Finally an overview of the use of biomarkers in the setting of stable angina will be explored and current evidence outlined.

1.1 Atherosclerosis

Coronary artery disease is predominantly caused by the process of atherosclerosis within the coronary arteries. The word atherosclerosis is based on the Greek words *athere* which can be translated as gruel and *skleros* meaning hard. The word itself is a simple description of the complex process of accumulation of lipid and thickening of the arterial intima.

Our understanding of the process of atherosclerosis is based on observations from epidemiology studies which have identified factors contributing to atherosclerosis. Inspection in vivo and in post-mortem studies of coronary and other arterial samples has enabled the development of a model of atherosclerosis, elements of which have been further defined by animal models. There is a vast amount of research and evidence on the subject of the pathogenesis of atherosclerosis and huge detail has emerged of the processes involved. Although an in-depth analysis is beyond the scope of this thesis a summary of the models published by Libby[1], Weber[2] and Falk[3] is described below.

As can be seen in Figure 1 the normal coronary arteries have three layers; from lumen outwards the tunica intima, tunica media and the adventitia. The inner most surface of the tunica intima is a single layer of endothelial cells that is in contact with the blood flowing in the lumen. It has been suggested that these endothelial cells respond to a trigger or insult such as hypertension, abnormal inflammatory mediators or lipids. This process is illustrated as a passive loss of endothelial barrier in response to injury whereby plasma molecules and lipoprotein particles enter the subintimal space. These lipoproteins are oxidised by enzymes likely to include myeloperoxidase, 15-lipoxygenase, and nitric oxide synthase (NOS) to become proinflammatory, chemotactic and cytotoxic. The enzyme Lp-PLA2 (lipoprotein-associated phospholipase A2) enters the intima bound to low density lipoprotein (LDL) and is also secreted by inflammatory cells, it hydrolyses oxidised lipoproteins to form bioactive lipid mediators that are thought to be chemotactic and also cytotoxic to macrophages. The endothelium responds by upregulating expression of adhesion molecules including

vascular cell adhesion molecule-1 (VCAM-1) on the lumen surface and secreting chemokines.[1]

Leukocytes (mostly monocytes) in the circulating blood then bind to these adhesion molecules and changes occur in the extracellular matrix and basement membrane with retention of low density lipoprotein (LDL).[4] This further stimulates leukocyte binding and, with chemokines such as Monocyte chemotactic protein-1 (MCP-1) encourage the monocytes to migrate into the intima and differentiate into macrophages as illustrated in Figure 1(2). These macrophages then absorb lipoprotein molecules that have accumulated and become foam cells, heavily laden with lipid. The foam cells internalise the lipoproteins by means of scavenger receptors SR-A and CD36. One can say that the key step now in the formation and growth of pathological plaque is the result of failure of the macrophages to remove the lipid from the vessel wall at this point by what has been coined reverse cholesterol transport. Unfortunately in atherosclerosis this mechanism fails as the scavenger receptors are not down-regulated by the accumulation of cholesterol within the cells and the foam cells remain in the intima and continue to accumulate lipid until they die either by apoptosis or necrosis, possibly with the involvement of Lp-PLA2. These foam cells and the debris of the dead cells forms a lipid rich core to the atherosclerotic plaque. The foam cells also extend the inflammatory process by the release of chemical mediators and contribute to the creation of a pro-thrombotic state by releasing pro-coagulant tissue factors.[1]

The inflammatory process of atherosclerosis is complex and many pathways, immune cells and receptors are involved. The adhesion molecules on the activated endothelial cells also bind a smaller number of T cells. T helper 1 cells can be activated by antigen presenting cells and secrete interferon-g which magnifies and sustains the inflammatory response in the media. Inflammation can also be initiated via Toll-like receptor 2 (TLR2) signalling by lipoproteins bearing apolipoprotein C-III (Apo-CIII) or apolipoprotein B (Apo-B).[1] Working to decrease the inflammatory process regulatory T cells produce anti- inflammatory cytokines interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) and a small number of B cells around atherosclerotic arteries may produce antibodies to attenuate the inflammatory process.[1]

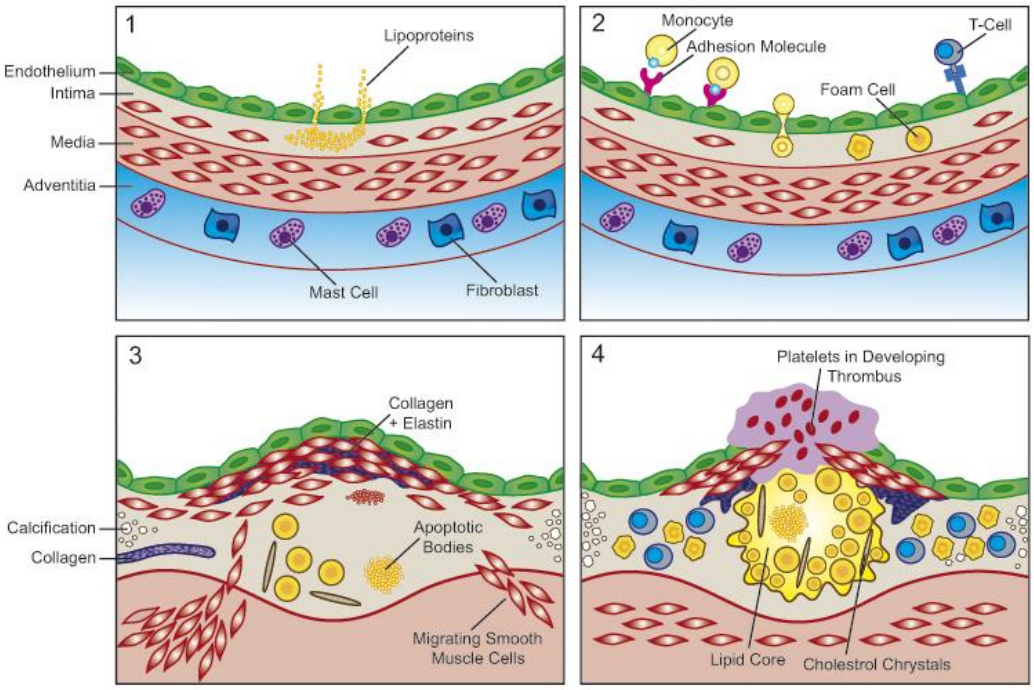


Figure 1 An overview of the atherosclerotic process. (1) Layers of normal arterial wall with lipoprotein entering through endothelium into intima. (2) Binding of monocytes, migration and differentiation and formation of foam cells. (3) Migration of SMC and formation of lipid core of plaque. (4) Rupture of plaque leading to thrombus formation. Adapted from Libby 2011.[1]

The third stage in atheroma development as seen in Figure 1(3) is the migration of smooth muscle cells from the tunica media to the intima where they proliferate and form a fibrous cap of collagen and elastin over the plaque. Some of the foam cells within the plaque die and the cellular debris accumulates to create a lipid rich core of the plaque.[1]

Some plaques, typically those with a thin cap with few smooth muscle cells[5, 6] and an active inflammatory process[7] may go on to rupture.[8] As can be seen in Figure 1(4), plaque rupture exposes a large quantity of thrombogenic material to the arterial lumen and can result in acute thrombosis and acute myocardial infarction. It will be demonstrated that this is a major cause of mortality and morbidity.[9]

Other plaques take a more indolent course with smooth muscle cells and fibroblasts creating a thicker, fibrous cap over the plaque reducing the chance of rupture. These lesions appear more stable, either exerting no significant physical effect or gradually encroaching on the arterial lumen until restriction of blood flow leads to symptoms such as angina pectoris. Over time the atherosclerotic process can lead to an increase in vessel size termed positive remodelling, whereby, despite increased atheromatous plaque, the vessel lumen can be maintained by increase in the overall size of the vessel.[10]

Calcification occurs in atherosclerotic lesions but the mechanism and significance are not fully understood.[11] The first evidence of calcification is seen in the second decade of life and calcification increases with ageing.[12] In a study of autopsy specimens early and small areas of calcification were found within the cytoplasm of cells and within the extracellular material in and near the lipid core of plaques. This is thought to originate from dead cells such as fibroblasts and smooth muscle cells[13] but it may also be due to osteogenic differentiation of senescent vascular smooth muscle cells.[14] The significance of this calcification is not fully understood, nor is it's relationship to plaque rupture which remains contentious.[15, 16] Calcification within the coronary arteries can be viewed as an indicator of the overall burden of atherosclerotic plaque within an individual and has been used as an indicator of cardiovascular risk.[17-19]

1.2 Morbidity and mortality in coronary artery disease

It has been shown that the development of coronary artery disease is a gradual process and in order to gain more understanding of the impact of coronary artery disease it is best to look at the consequence of the process and the morbidity and mortality caused by it. Coronary artery disease leads to many disease states and the major ones are outlined below.

Table 1 Morbidity and mortality in coronary artery disease

Coronary artery disease causes death by:

- Cardiac failure
- Cardiac arrhythmias
- Mechanical failure such as ventricular rupture or valvar incompetence.

Coronary artery disease causes morbidity by:

- Cardiac failure and limitation of functional capacity
- Myocardial Ischaemia leading to angina pectoris
- Recurrent arrhythmias

Coronary artery disease is a major cause of morbidity and mortality worldwide. The World Health Organisation (WHO) estimates that 7.2million people died in 2004 from coronary artery disease,[20] this represents approximately 4% of all deaths globally. As traditional causes of death such as malnutrition and infectious disease decline and risk factors for coronary artery disease rise worldwide the WHO estimates that this will continue to increase with heart disease and stroke predicted to remain the single leading causes of death worldwide. In Europe coronary artery disease is the biggest cause of death, responsible for 22% of all deaths.[21]

It is harder to quantify morbidity from coronary artery disease than mortality but in the 2006 Health Survey for England 3.4 million adults reported suffering from angina or a heart attack.[22] This is likely to be an underestimate for prevalence of angina and myocardial infarction and does not include those living with symptoms of heart failure as a result of coronary artery disease. The Heart of England study screened patients using a combination of clinical examination and echocardiography data and suggests that there are over 700,000 people over the age of 45 in the United Kingdom (UK) with 'definite heart failure'[23] with coronary artery disease being the cause in approximately 70% of patients.[24, 25]

In recent years in the UK there has been greater success in treating patients with myocardial infarctions and a reduction in the mortality rate, however the corollary to this is that there is an increasing burden of chronic heart failure.

It can be concluded that coronary artery disease will continue to have a considerable impact on mortality and morbidity worldwide for many years to come.

Coronary artery disease can remain asymptomatic or manifest itself to the medical profession in a variety of ways from angina to sudden death. The disease can present for the first time in a previously asymptomatic individual with an acute myocardial infarct or with gradual development of angina, or with heart failure symptoms. Approximately 50% of patients presenting with acute myocardial infarction have no previous symptoms.[26] In a large proportion of these patients acute myocardial infarction leads to death or heart failure in spite of contemporary treatment strategies including primary percutaneous revascularisation and thrombolysis. The challenge therefore is to try to identify these patients at an earlier stage where the disease process can be modified and the long term sequelae prevented.

1.3 Treatments for coronary artery disease

The medical approach to coronary artery disease has many facets. Public health interventions are aimed at reducing the development of coronary artery disease in the general population and there have been measures to address some of the risk factors that lead to atherosclerosis in relation to smoking cessation, exercise and diet. The identification and treatment of groups likely to develop significant atherosclerosis and suffer with its consequence is another key aspect; hypertension, diabetes, hyperlipidaemias are all addressed by medical and non-medical means.

In individuals who present with symptoms related to coronary artery disease there is a wide range of presentations and treatment strategies. The main presentations are; acute coronary syndromes, stable angina, heart failure and arrhythmias.

In patients who present with acute coronary syndromes the mainstay of treatment is revascularisation and secondary prevention. Each patient is risk stratified depending on their individual case and consideration given to the likely risks and benefits of

revascularisation versus medical secondary prevention alone. Acute coronary syndromes are largely split into three further groups although various terms and classifications are used; ST elevation myocardial infarction, Non-ST elevation myocardial infarction and unstable angina. ST elevation refers to the characteristic changes seen on electrocardiogram (ECG) that suggest ongoing infarction of myocardial cells.

In acute ST elevation myocardial infarction, there is abrupt occlusion of a coronary artery by thrombus and prompt re-opening of the occluded artery is required to prevent extensive myocardial infarction and the subsequent heart failure and arrhythmic consequences. In contemporary practice this is accomplished by means of either the administration of thrombolytic drugs or by immediate percutaneous coronary intervention (PCI) widely called 'Primary PCI.' In primary PCI catheters are manipulated within the arterial system and placed at the ostium of the affected coronary artery, through these catheters various devices can be deployed to aspirate thrombus and dilate the coronary arteries in an attempt to restore flow down the artery. In the current era primary PCI usually results in the placement of a coronary stent, a mesh metal tube designed to scaffold the coronary artery. Patients treated with thrombolytics are also usually then assessed by means of coronary angiography and undergo revascularisation.

Patients with other acute coronary syndromes are risk stratified depending on their presentation, ECG findings, and biomarkers such as troponins which are released from the heart during infarction. A large number of these patients considered at high risk then go on to have further assessment usually by means of coronary angiography and then will undergo revascularisation by either PCI with the placement of coronary stents or by coronary artery bypass grafting (CABG). CABG is a significant operation that involves the placing of conduits such as redirected internal mammary arteries and reversed saphenous veins to provide an alternate supply of blood to the distal coronary arterial tree, bypassing proximal occlusions or stenoses.

Patients with stable angina symptoms are treated with a range of medical therapies such as beta-blockers, nitrates, calcium channel blockers and other medications

designed to improve myocardial blood flow or reduce myocardial oxygen demand. These are prescribed in conjunction with medications and interventions such as smoking cessation designed to reduce the further development of atheroma and reduce the risk of subsequent myocardial infarction. This can be an effective strategy in a large number of patients but many are refractory to medications and require revascularisation to improve their symptoms. As in acute coronary syndromes, revascularisation can be either PCI or CABG.

The treatment of heart failure patients requires a combination of medical therapies, devices such as cardiac resynchronisation pacemakers, exercise training and even cardiac transplantation. This requires provision of an extensive service with staff from many disciplines and places a significant burden on the health care system.

Patients with arrhythmias as a result of coronary artery disease often have heart failure and there is significant overlap in their therapy with the use of devices such as pacemakers and implantable cardiac defibrillators and the use of anti-arrhythmic medications.

Thus it can be seen that the treatment of patients with coronary artery disease results in the prescription of medications for disease modification and symptom control and a large number of patients undergo the placement of cardiac stents, bypass surgery or implantation of cardiac devices.

1.4 In-stent restenosis

Coronary artery stenoses are often treated by means of percutaneous dilatation using small balloons within the coronary arteries to dilate the artery at the point of stenosis. In contemporary practice this technique is usually augmented by the placement of stents within the coronary arteries to overcome elastic recoil. These are metal alloy stents with a mesh structure that can be introduced into the coronary arteries mounted on a balloon and dilated to achieve apposition to the vessel wall. These stents can be coated in a drug eluting polymer to try to reduce the extent of restenosis

within the stent. Restenosis after coronary stenting, defined by ≥50% luminal loss, occurs in about 10- 20% of cases in the first 12 months and usually presents with recurrent chest pain.[27] The assessment of patients with existing coronary stents is a growing area with over 30% of diagnostic procedures performed in this setting and with the increasing use of coronary stents, this number is likely to increase.

1.4.a The development of in-stent restenosis

Initially coronary interventions were performed using balloons to dilate lesions within the coronary arteries. There was a high level of restenosis in patients undergoing these procedures. Intravascular ultrasound (IVUS) and histopathological examination found that 75% of the restenosis was due to elastic recoil or negative remodelling and 25% due to the development of new plaque within the treated area (neo intimal proliferation).[28, 29] After the use of stent implantation the mechanical factors were virtually eliminated leaving neo-intimal proliferation as the main cause of restenosis.[30, 31] Neo-Intimal proliferation is caused by arterial injury which leads to platelet activation and inflammation via the action of mediators such as growth factors and cytokines. This leads to proliferation and migration of vascular smooth muscle cells and the synthesis and secretion of extracellular matrix and cytokines by the vascular smooth muscle cells that together form the neo-intima.[32]

1.4.b Assessment of suspected in-stent restenosis

There are several different ways a patient returning with stable chest pain after coronary stenting can be assessed. The central division in assessment strategy after clinical assessment is that between either anatomical assessment or assessment of ischaemia. Currently invasive coronary angiography is the only technique widely employed for the anatomical assessment of these patients. Ischaemia can be assessed by means of stress echo, nuclear imaging, perfusion MRI or less commonly now exercise ECG. The assessment strategy used is defined by the pre-test probability for ischaemia based largely on the history with an anatomical strategy with invasive

coronary angiography (CAX) employed in patients thought likely to have significant coronary stenoses. A number of patients with atypical chest pain are likely to be assessed first by an ischaemia test but it is not uncommon for a combination of anatomical and ischaemia measures to be used.

1.4.b.i Invasive coronary angiography

Invasive angiography is a procedure by which x-ray contrast medium is injected directly into the coronary arteries and two dimensional images are obtained from various angles in an attempt to fully visualise the coronary anatomy. In order to inject contrast media directly into the coronary arteries the operator needs to gain access to the arterial circulation usually by puncturing the radial or femoral artery and introducing a sheath that allows passage of further devices into the arterial system. The operator then introduces small specially shaped tubes (catheters) 2-3mm diameter, into the arterial circulation and by the means of careful manipulation and the use of x-ray guidance, positions the catheter at the ostium of each of the coronary arteries in turn. The procedure is resource intensive and requires skilled operators with the support of a catheter laboratory team.

The procedure of invasive coronary angiography is a widely performed procedure, both for the assessment of native coronary artery disease and for the assessment of patients with prior coronary artery bypass grafts and previous stenting. However the procedure does have some risk associated with it. Although the majority of data come from an earlier era it is thought that the true risk of a diagnostic coronary angiogram is between 1 and 2%.[33, 34] These complications include bleeding, usually related to the site used to access the arterial system, stroke, myocardial infarction and death, common to other contrast reliant x-ray techniques such as CTCA there is also a small chance of anaphylactoid contrast reaction or contrast induced nephropathy, which; although usually transient, can result in permanent renal failure.

Invasive coronary angiography only allows visualisation of coronary anteries by the contrast injected filling the arterial lumen and blocking the passage of x-rays. Thus invasive coronary angiography only provides information about the coronary artery

lumen and has sometimes been called lumenography. It is possible to gain some additional information through visualisation of dense calcification in the coronary arterial tree or visualisation of the outline of coronary stents, although calcification is not always apparent via angiography and it can be hard to visualise some stent types.

Invasive angiography also only provides a planar, two dimensional view of the coronary artery, and whilst images can be obtained from a range of angles there can be problems with overlapping arteries and the technique cannot fully delineate the three dimensional nature of coronary plaque. Coronary arterial plaque is often eccentric and this can lead to misleading appearances on coronary angiography that generally leads to underestimation of lesion severity. It has long been recognised that there are limitations to the accuracy of the technique of coronary angiography, specifically related to underestimation of disease severity when compared to post-mortem studies and intra-operative flow studies.[35-38] Coronary angiography has also been shown to have a high interobserver and intraobserver variability.[39, 40]

1.4.b.ii Intravascular ultrasound (IVUS)

Invasive coronary angiography is generally considered the clinical standard for assessment of coronary artery disease and in-stent restenosis, as described above it is becoming increasingly recognised that this technique has weaknesses and in fact when stents are assessed by intravascular ultrasound (IVUS) or optical coherence tomography (OCT), there can be significant discrepancy between the angiographic findings and the IVUS or OCT findings.[41]

IVUS and OCT techniques provide tomographic images from a probe within the coronary artery, providing a much higher spatial resolution image than invasive angiography, and overcoming the problem of overlapping vessels. In IVUS the probe is a miniaturised ultrasound probe that takes a tomographic image of the coronary artery and in OCT a similar cross-sectional image is obtained by the use of near-infrared light.

IVUS uses high frequency sound waves reflected off the coronary arterial wall from within the lumen. The technique has a spatial resolution of 100-200μm and a tissue penetrance sufficient to image the full depth of a coronary artery wall. OCT has a

much higher spatial resolution of 10-20μm but has a lower penetrance of 1-3mm in tissue.[42] OCT also is sensitive to scatter from red blood cells and requires a blood free field within the lumen so the vessel must be flushed to fill it with contrast during image acquisition. IVUS is the most widely available of these two techniques in clinical practice and is the modality that will be investigated later in this thesis.

IVUS was first proved in the 1980s and 1990s at a time when it was apparent that there was significant intra-observer and interobserver variation with coronary angiography and discrepancy between coronary angiograms and post-mortem examination and the realisation that the angiographic severity of stenoses was a poor predictor of physiological severity.[37, 38, 40, 43] Technology has greatly improved since the early years of IVUS by increasing the transducer frequency and power which improves image quality and miniaturising the probes allowing smaller vessels and more severe stenoses to be assessed.

IVUS is more invasive than diagnostic coronary angiography due to the need to pass guide wires into the lumen of the coronary artery being assessed and the passage of a probe into the artery itself. They thus have a slightly higher procedural risk than diagnostic angiography alone. In the multicentre survey by Haussman[44] of 2207 procedures it was identified that IVUS was predominantly associated with coronary spasm with 2.9% of patients suffering transient spasm and more serious complications such as acute vessel occlusions, dissections, and/or embolism in 0.4 % of the patients although they could not all be directly attributed to the IVUS procedure and may have occurred with diagnostic angiography alone. In Batkoff's study of 718 IVUS studies the complication rate including both spasm and major complications was 1.1% but these all occurred in patients undergoing coronary angioplasty.[45] In the abstract presented by Gorge,[46] spasm occurred in 3% of all patients and there was a 0.14% complication rate consisting of coronary artery dissection, thrombosis, ventricular fibrillation and severe spasm.

IVUS reveals more about the three dimensional nature of plaque than invasive coronary angiography and has been used to track changes in coronary arterial plaque in response to medical therapies.[47]

In-stent restenosis is often seen as very short segments of stenosis (<1mm)[48] which can be missed by conventional angiography. The IVUS probe within the vessel is more likely to detect the area of greatest narrowing. Angiography only allows a measurement in variations of luminal diameter of stented and adjacent non stented areas and provides only an indirect measure of in-stent neointimal hyperplasia and cannot account for positive remodelling.[49] Stent struts are well visualised by IVUS and the relationship of tissue to the stent can be accurately established, this is not possible with conventional angiography as it can be very difficult to visualise stents and even harder to tell the relationship of tissue to the stent. IVUS is now widely used as the gold standard for assessing in stent restenosis and hyperplasia, particularly when comparing different coronary stents and also provides other important information such as adequacy of stent deployment, apposition to vessel wall and accurate sizing which are important in reducing in-stent thrombosis.

1.5 CT coronary angiography

Invasive coronary angiography is currently the clinical standard for assessing coronary artery stenoses. It has excellent spatial and temporal resolution and allows for percutaneous intervention at the same sitting. However as described earlier, invasive angiography can be associated with serious complications and may reveal non-obstructive disease that does not lead to an intervention. Invasive coronary angiography without adjunctive techniques cannot image the vessel wall and assess plaque characteristics. There has, therefore, been great interest in developing non-invasive methods of performing coronary angiography and assessing plaque morphology.

Coronary arteries are difficult to image because they are small and move not only with the cardiac cycle but also with respiration. Non-invasive imaging of these structures needs a technique that produces high spatial and temporal resolution and that also

compares well with the current gold standard. Technological advances (both hardware and software) in computed tomography (CT) imaging over the last few years have made it an appealing technique for providing non-invasive images of coronary arteries.

In the following section the process of cardiac CT will be summarised and some of the unanswered questions will be highlighted.

1.5.a History

In 1895, William Röntgen (a German physicist) produced and detected electromagnetic radiation in a wavelength range today known as X-rays or Röntgen Rays. Whilst investigating materials that could stop these rays he passed his hand in front of the X-ray source and produced the first X-ray image. He was awarded the Nobel Prize for Physics in 1901 in recognition of "the extra-ordinary services he has rendered by the discovery of the remarkable rays subsequently named after him".[50] Clinical CT itself was invented by Godfrey Hounsfield in 1972. He also received the Nobel Prize (for medicine) in 1979 along with Allan Cormack and in his acceptance speech stated that "…. a further promising field may be the detection of the coronary arteries…."[51]

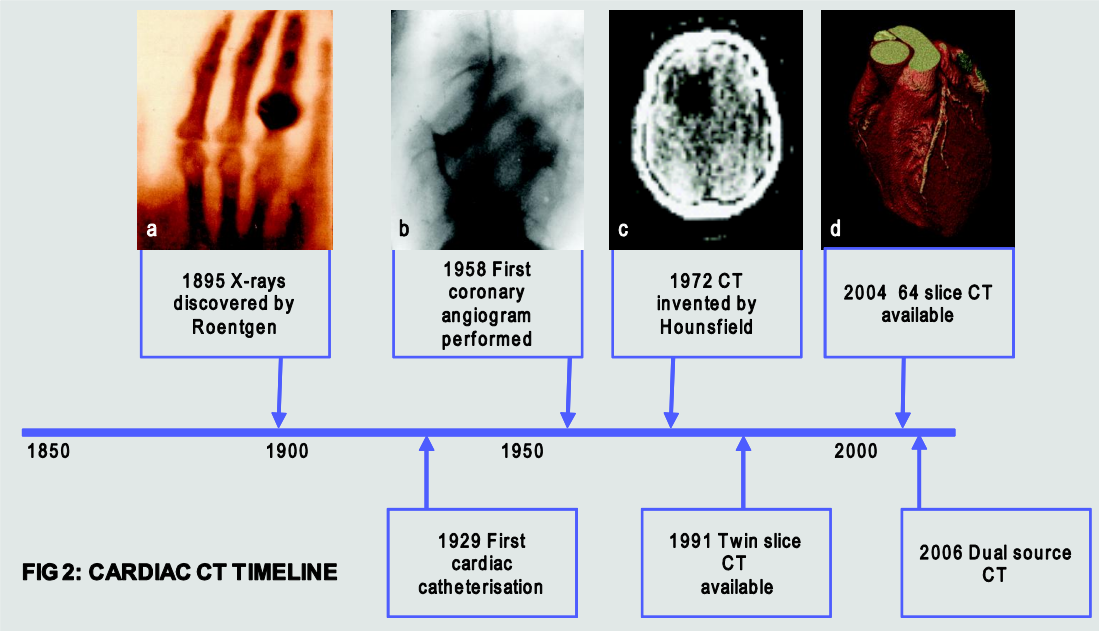


Figure 2 Timeline of the development of cardiac CT

Initial CT scanners were limited to tomographic sections of the brain that took several minutes to acquire. Slip ring technology replaced the cables of older scanners and permitted fast spiral scanning whereby the X-ray source and detector continuously rotate around the patient whilst the patient table moves through the scanner. The scan speed was further improved by changing the shape of the radiation beam (to a fan shape) and increasing the number and quality of X-ray detectors in what are called multi-detector (or multi-slice) CT scanners (Figure 3). Developed in 1991, the Elscint CT Twin was the first multi-slice (MSCT) scanner and had two parallel banks of x-ray detectors to acquire two slices per gantry rotation. Quickly the technology developed with scanners with 4 slices, then 16 slices, and current scanners having 64 slices with 320 slice scanners available.

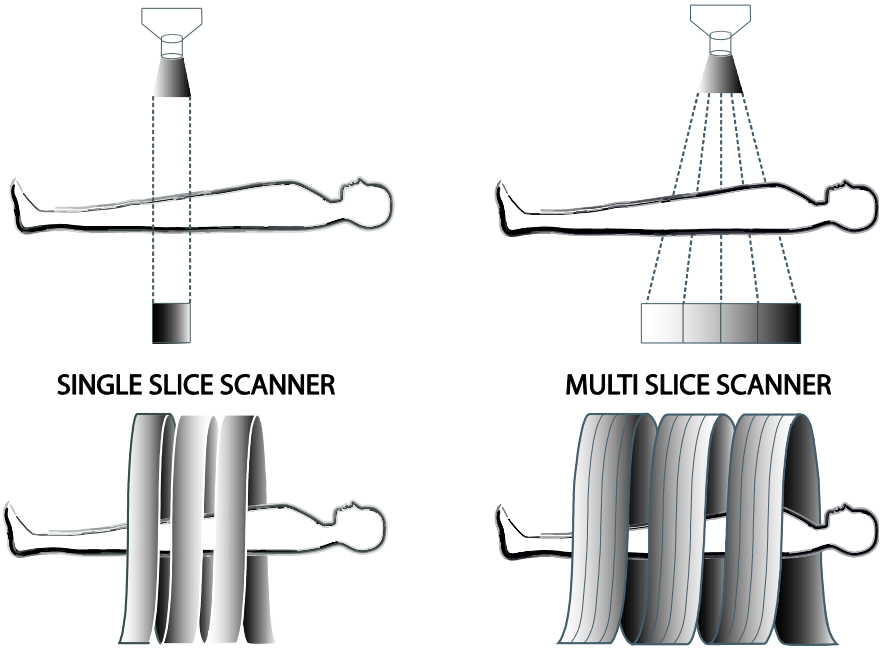


Figure 3 Comparison of single slice and multi slice CT scanners

Recently the first dual-source MSCT was launched.[52] This has two pairs of X-ray sources and multi-slice detectors mounted at 90 degrees to each other (Figure 4).

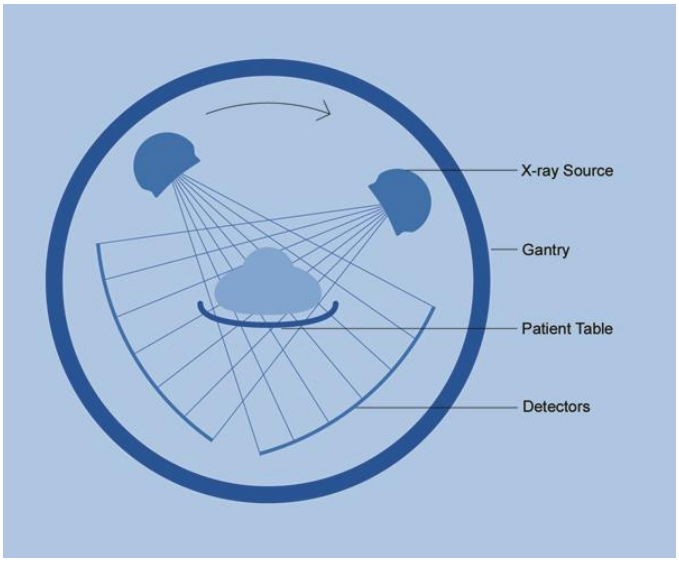


Figure 4 Diagram illustrating concept of a dual source CT scanner.[53]

This produces faster scanning and achieves a temporal resolution of 75ms. The effect of multiple slices, faster rotation times and dual-source technology on spatial and temporal resolution is shown in Table 1. The data in the table only consider the temporal resolution available from CT scanners using single sector reconstructions. Several manufacturers use multi sector reconstructions to obtain faster theoretical temporal resolutions and this will be discussed further in the technology section. There are limited independent data on the true spatial resolutions obtained during cardiac scans.

Table 2 Comparison of temporal and spatial resolution of different coronary imaging modalities

	Spatial Resolution (mm)	**Temporal Resolution (ms)**
Invasive Angiography	0.2	5-20
Electron Beam CT[54]	>0.6	33-100
16-Slice CT	0.5	200
64-Slice CT [55]	0.4	165
Dual-Source 2 x 64-Slice CT [52]	0.4	75
Magnetic Resonance Angiography [54]	0.7	20

Electron-beam CT (EBCT) was launched in 1990. It provided very high temporal resolution due to the electronic sweeping of the electron beam which can be completed much faster than the mechanical rotation of multi-slice CT. EBCT has been extensively used in calcium scoring of coronary arteries[17] but suffers from poor spatial resolution. Multi slice CT can now perform accurate calcium scoring[56] and is more widely available than EBCT which will not be addressed further here.

1.5.b CT Technology

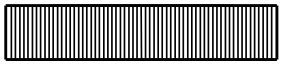
CT scanners have an X-ray source (tube) and sensors mounted on opposite sides of a gantry that continuously rotates around the patient. Scans are then taken as the patient moves through the gantry. Computer systems can process these data to generate three-dimensional volumetric information, which is in turn viewable from multiple different perspectives on attached CT workstation monitors.

1.5.b.i Spatial resolution and coverage

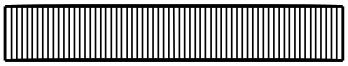
The image obtained on the monitor is made up of a series of 3D pixels (or voxels) the size of which depends on the scanners spatial resolution. The voxel itself displays a shade of grey (from black to white) depending on the average attenuation of the tissue within the voxel. Bone and (importantly for cardiac scanning) calcium have high attenuation values (Hounsfield Units) and are displayed as white. Air has a low attenuation value and is displayed as black. Unfortunately, if a voxel within a coronary artery contains calcium and a tissue with a low attenuation signal (eg a fatty plaque), the whole of the voxel will be displayed as white and the useful information is lost. This accounts for 'partial volume' effects seen in CT. The smaller the voxel size, therefore, the less partial volume effects will be seen and the spatial resolution will be better. Voxel size is dependent on the resolution of the X-ray sensors, not the number of slices.

To increase the speed at which an area of interest such as the heart can be scanned (thereby reducing the length of breath-hold), more recent scanners have an array of x-ray detectors covering a larger area and collecting data from multiple 'slices' per rotation of the scanner. The size of the array is dependent on the size and number of individual detectors. Increasing the size of detectors would result in a worse spatial resolution, thus if spatial resolution is to be maintained, larger arrays require more detectors. The time it takes to scan an area of interest is dependent on the area covered by the detector array, the rotation speed and the speed at which the patient passes through the scanner (termed the 'pitch'). Figure 5 illustrates several available

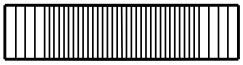
arrays, fixed arrays have evenly spaced detectors and adaptive arrays have a combination of detectors of varying sizes that can be used in different configurations.



Fixed array 64 x 0.5mm Detectors, 32mm Z-coverage



Fixed array 64 x 0.6mm Detectors, 40mm Z-coverage



Adaptive array 32 x 0.6mm, 8 x 1.2mm Detectors, 28.8mm Z-coverage

Prototype fixed array with 256 x 0.5mm Detectors, 128mm Z-coverage

Figure 5 Fixed and adaptive arrays, showing variation in detector size

Some scanners use an alternating focal spot technique to increase the number of slices. The x-ray beam from the source rapidly alternates between two points (Figure 6), resulting in double sampling of the detectors to effectively achieve double the number of slices. The disadvantage is that in this mode the coverage of the array tends to be less and thus requires more time to scan the heart than a larger detector, the signal to noise ratio is also lower and thus higher radiation doses are required.

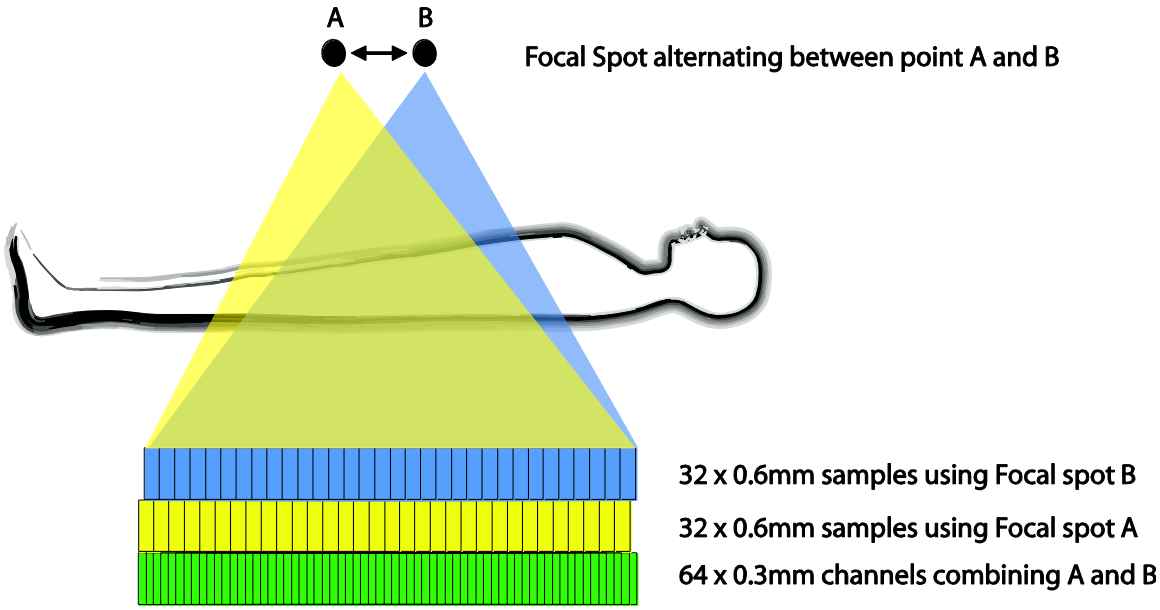


Figure 6 The alternating focal spot technique to increase spatial resolution

1.5.b.ii Temporal resolution

In order to image the coronary arteries, the heart needs to be as stationary as possible. Respiratory motion is excluded by performing the scan during a breath-hold and cardiac motion is limited by obtaining images when the heart is at its least mobile during diastole. The temporal resolution of CT scanners is essentially determined by the speed of rotation of the gantry around the patient. As it is possible to accurately reconstruct images using data acquired from a 180 degree rotation rather than the full 360 degree rotation, the temporal resolution is equal to half the gantry rotation speed. A small allowance should also be made for the fan angle in calculating temporal resolution, but the major determinant, varying between scanners is the rotation speed. Some CT scanners utilise partial scan reconstructions to increase quoted temporal resolution. Using this technique data from adjacent cardiac cycles are used to reconstruct one axial data set. For example by combining the data from two adjacent cycles the temporal resolution can be dropped to a quarter of the rotation speed (Figure 7).[57] In vivo studies show that two-segment reconstruction can slightly improve diagnostic sensitivity in heart rates >65bpm.[58] The problem with this

technique is that it assumes that the coronary artery always returns to exactly the same position in each cardiac cycle. As this is not the case, although the temporal resolution is quoted lower, the resulting image contains potentially more error and artefact. This technique must therefore be used with caution and is not a substitute for improving the true temporal resolution of a machine.

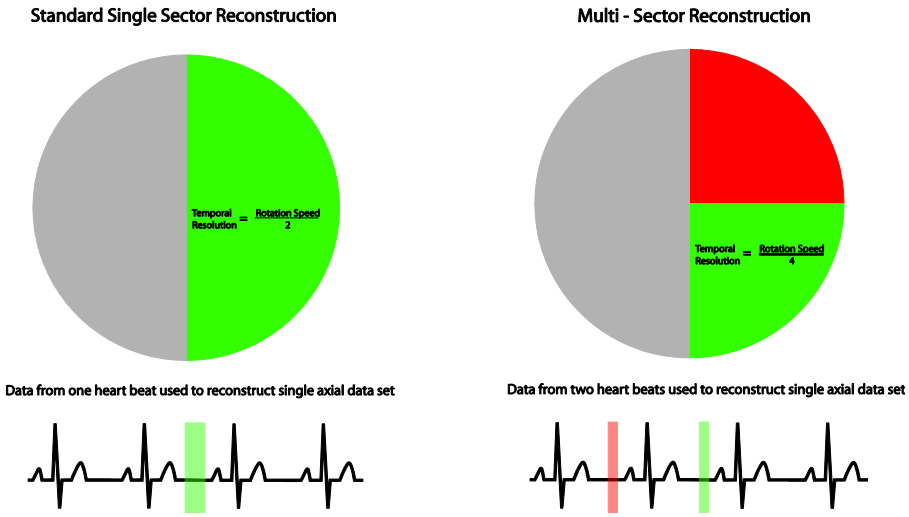


Figure 7 Theoretical temporal resolution with single and multi-sector reconstructions

The rotation speed of the gantry has been increased over the last few years to 250ms per rotation but as the speed increases further the logarithmic relationship between speed and centrifugal forces makes it increasingly hard to achieve faster rotations. A novel approach to overcoming this hurdle and effectively halving the temporal resolution is to put two ct scanners inside the same gantry at right angles to each other (Figure 4). This design halves the amount of time required to gather data from 180 degrees around the heart, reducing the temporal resolution to 75ms, permitting accurate imaging at higher heat rates and less motion artefact.

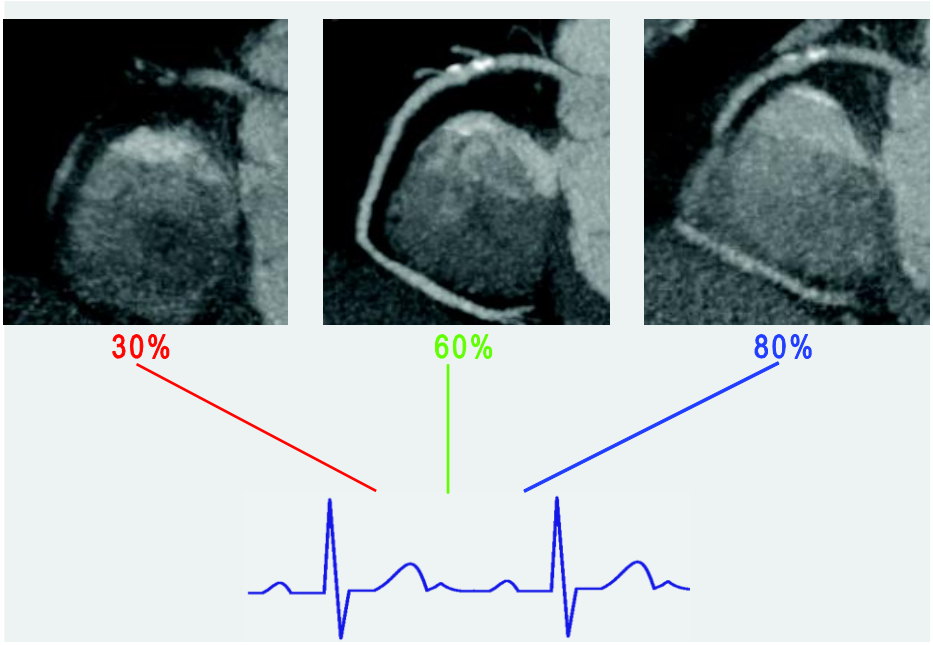


Figure 8 Effect of reconstruction at different points in cardiac cycle represented as % of rr interval from initial qrs

1.5.b.iii ECG gating

Depending on the coverage of the x-ray array, and to a lesser extent the pitch and rotation time, it takes around 6-12 seconds for a 64 slice CT scanner to cover the whole of the heart and so the coronary arteries need to be reconstructed from data obtained from multiple heart beats. With larger detector arrays the heart can be covered in 1 or two cardiac cycles. ECG gating enables us to use only the data from certain parts of each consecutive cardiac cycle to generate useful images and typically targets the acquisition or reconstruction of images to the period in the cardiac cycle when the heart is least mobile and thus least prone to imaging artefact (Figure 8).

In prospective gating, the R-wave on the ECG is recognised, there is a time delay and then scanning starts, stopping after a certain period to resume at a similar time during the next cycle. Although this technique, when coupled with repeated axial acquisitions rather than a continuous spiral, has the potential to greatly reduce dose it is limited by the fact that a single ectopic beat or other arrhythmia may lead to the scanner starting at times when the heart is in a different position in the chest. In addition, if the time delay picked is not optimal, image quality will again suffer. As detector arrays with

greater coverage become more commonplace in clinical practice prospective gating has become more frequently applied. Less commonly implemented in modern scanners, though implemented in many of the initial 64 slice scanners is retrospective gating, when data are collected continuously throughout the cardiac cycle as the patient moves constantly through the scanner, and later reconstructed at an appropriate time interval (Figure 9). This can be quoted as a percentage of the RR interval (e.g. 65%) or as an absolute value (e.g. 700ms). The actual phase used can vary for each coronary artery and between patients. Several different phase reconstructions may be required to obtain optimal images of all vessels.

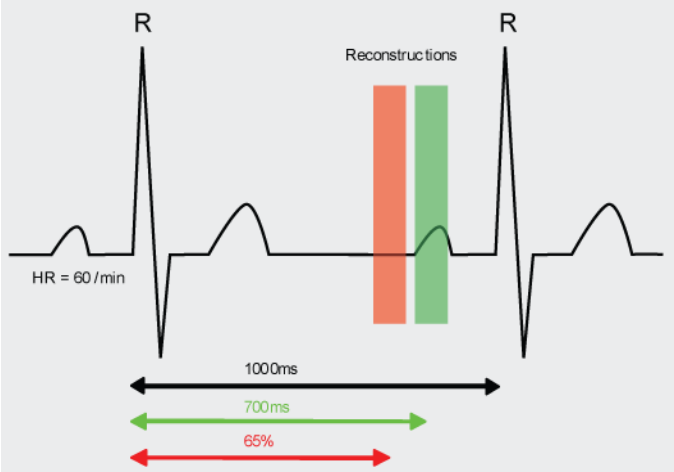


Figure 9 Methods of defining retrospective gating reconstruction timing

1.5.b.iv Performing a scan

Here the procedure of undertaking a CTCA scan is described as it applies to the most commonly available 64 slice scanners. Patients do require some preparation prior to their non-invasive coronary angiogram. Firstly, there are a number of contra-indications which are applicable to any contrast CT. In addition, there are several circumstances when cardiac CT may not be appropriate (Table 3). Note that dual source scanners, due to the higher temporal resolution, can permit the scanning of patients with irregular rhythms and reduce the need for beta blocker administration.

Table 3: Exclusion criteria for CTCA

Contraindications to Contrast Enhanced CT

- Renal failure
- Inability to lie flat
- Contrast allergy
- Caution in pregnancy

Causes of Excessive Artefact in Cardiac Scans

- Irregular heart beat (AF, frequent ectopics)
- Inability to breathold
- Tachycardia
- (Pacing wires and metallic valves)

An intravenous cannula is required for the contrast injection. To slow the heart beat and improve image quality a β-blocker (eg oral metoprolol 100mg) may need to be given an hour before the scan if the patient is not naturally bradycardic. It is common to aim for a heart rate below 65 beats per minute. Patients intolerant of β-blockers can be given a calcium channel blocker. The patient is placed in the CT scanner and attached to an ECG and contrast injector. Many centres also advocate the use of sublingual nitrate prior to scanning as this can improve coronary artery visualisation.[59] A scout X-ray is taken to ensure correct alignment of the patient and after some practice breath-holds the scan is performed. Depending on clinical question, a calcium score is sometimes carried out first and those patients with a high calcium score (>400 Agatston units) may not be studied further because of reduced specificity. The start of the scan needs to be timed with the arrival of contrast in the ascending aorta. This can either be done automatically with the CT triggering once the Hounsfield unit of a region of interest in the aorta crosses a threshold due to the arrival of the contrast, or manually after measuring the contrast agent transit time in a separate step, using a 'test bolus' of a small amount of contrast. The total volume of contrast given is of the

order of 50 – 100mls and the whole scanning process is complete after 10 to 15 minutes. Depending on the availability and robustness of implementation in your particular scanner; techniques that reduce the radiation dose such as 'dose modulation' should be used where possible. Scans are usually performed in the craniocaudal direction, however when larger areas need to be covered in the presence of coronary artery bypass grafts, it is possible to scan in the opposite direction, giving priority to the native vessels so that the grafts are towards the end of the breath-hold.

The large amount of data obtained need to be reconstructed (using the appropriate phase of the cardiac cycle as described above in the ecg gating section) and then analysed. Different reconstruction algorithms or 'kernels' are used to convert the raw data from the spiral scan raw data into interpretable images. Different kernels can be used in different situations with sharper but noisier kernels used to reduce blooming artefact in the presence of calcification or stents.

The software used to assist the clinician in interpretation is almost as important as the scanner itself. The raw, cross-sectional images are often reviewed first as these are often sufficient for diagnosis and also give information about the rest of the thorax (pericardium, mediastinum, aorta, lungs) which may harbour other unsuspected pathology.[60-62] The coronary arteries themselves can be assessed through these raw axial images, but further reconstructions are made to aid analysis.

The intensity of x-rays received by the detectors for an individual voxel (Hounsfield values) generated by the scanner are converted into greyscale to allow interpretation by the human eye with white areas representing high Hounsfield values and dark areas lower values. However the range of Hounsfield units generated from a CT scan is greater than the range of greys that the human eye can easily distinguish, thus 'windowing' levels have to be set to map a relevant range of Hounsfield numbers to a grey scale. There are two relevant parameters; the window width and the centre. The centre defines the mid-point of the Hounsfield scale used and the window width determines the range of Hounsfield values used to determine the grey scale with all Hounsfield values above the upper limit displayed as white and below the lower limit

black (Figure 10.) Different window settings have profound effect on the images displayed and different values are used to interrogate different tissues.

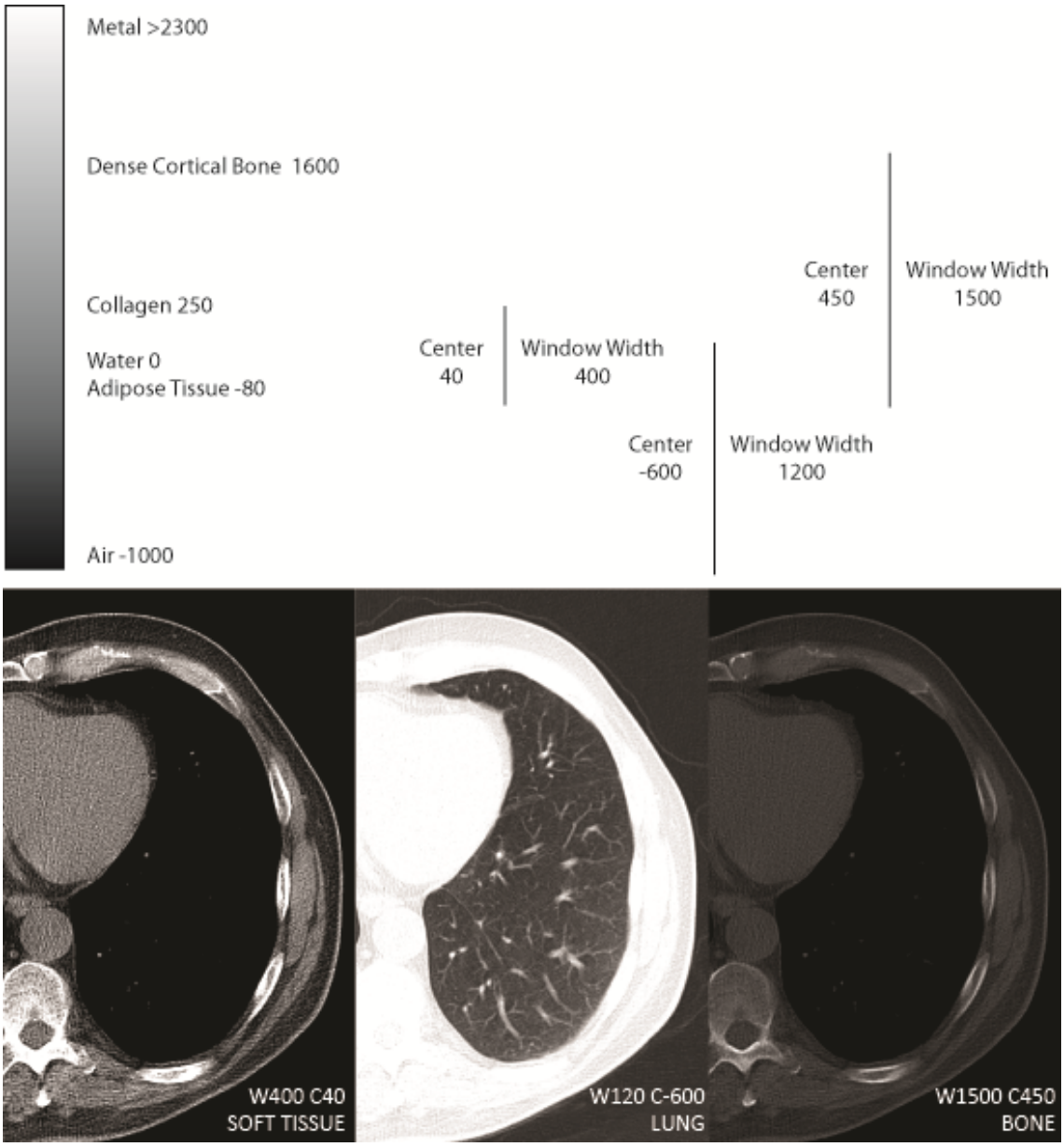


Figure 10 Effect of using different window levels when viewing CT images as greyscale. Top scale shows typical Hounsfield units for various materials. The images below demonstrated the effect of applying the different windowing levels and centres on image appearance.

The standard reconstructions used are multiplanar reformation (MPR) and maximum-intensity projection (MIP) (Figure 11). In MPR (Figure 11b) a straight or curved plane is

defined and only the data in this plane are displayed, this can be used to 'stretch out' a vessel and view it from many angles. The MIP algorithm (Figure 11a) displays only the highest-attenuation voxels taken from a slab through the 3D data for each pixel in the resulting image. Some software also enables the quantification of LV function and plaque composition. Volume rendering techniques produce visually pleasing images but these are generally only of clinical use in visualising bypass grafts or coronary anomalies.

Figure 11 Comparison of MPR and MIP reconstructions. The appearance of a stent in the left main coronary artery and left anterior descending artery is demonstrated with (A) MIP and (B) MPR reconstructions.

1.5.c Limitations with the technique

1.5.c.i Radiation dose

The main drawback with CTCA is the radiation dose. This was quoted as 10 – 15 mSv for a non-invasive angiogram in the scanner available for my research (around double the dose of a conventional angiogram).[63] I collated data on radiaton dose in 30 subjects at the beginning of our experience with CTCA demonstrating a mean dose of 12mSv (standard deviation 3.74mSv). It is difficult to correlate risk of medical radiation exposure but this probably equates to a lifetime risk of developing a malignancy of 1 in 1200.[64, 65] In contemporary practise widespread adoption of prospective gating which is more robust with large detector arrays or by lowering the X-ray power during less important parts of the cardiac cycle (eg systole) – this is termed "tube current modulation" or "dose modulation." There is evidence that the radiation dose can be reduced to 5-6mSv whilst not impacting on diagnostic quality of the scans.[66, 67] The additional radiation exposure should be considered in the context of the greater risks from the invasive nature of the conventional coronary angiogram[68, 69] and is similar to other CT scans performed on a routine basis. In the most recently available scanners employing larger detectors and using iterative reconstruction, considerably lower doses can be obtained,[70] with some centres reporting routine sub millisievert doses [71]although in published studies there is still a large range in the doses reported from different centres even using identical scanners. [72]

1.5.c.ii Cardiac arrhythmias

As stated earlier, patients with tachycardia or irregular heart beats (atrial fibrillation, extrasystoles) often provide non-diagnostic images and can not be accurately studied with this technique, although the higher temporal resolution of dual source CT makes assessment in more of these patients possible.

1.5.c.iii Inability to perform intervention

CTCA is most employed in patients with low likelihood of CAD due to the excellent negative predictive value that has been demonstrated. In those found to have significant disease one of the major benefits of invasive angiography is the ability to

perform intervention in the same sitting. Patients who have a non-invasive angiogram and then require PCI will have a potentially larger radiation dose with little clinical benefit.

1.5.c.iv Assessment of flow

Cardiac CT is not capable of assessing rate or quantity of flow across valves but can be used to measure valve orifice areas.[73, 74]

1.5.c.v Interpretation

Historically, cardiologists have taken control of cardiac imaging (catheterisation and ultrasound). However, radiologists receive specific training in CT and the vast majority of scanners are located in radiology departments. Consideration must be given to the need for trained interpretation of the non-cardiac structures which may take the form of a secondary review by a radiologist if the CT coronary angiograms are primarily reported by cardiologists. It is also important to consider what burden and benefits there are in identifying these incidental findings. Local factors in the UK influence the provision of CTCA services with variations in input from radiology and cardiology depending on local circumstances.

1.5.c.vi Training

Despite the introduction of specific training criteria and the work of societies within the United Kingdom to stimulate and organise training programs there is currently limited access to cardiac CT expertise and many other countries have not yet created local training guidelines. Ideally these programs should be run as part of a joint service between radiology and cardiology and trainees from both disciplines should receive training in non-invasive cardiac imaging.[75, 76]

1.5.d Competing technologies

1.5.d.i Magnetic resonance imaging

MRI is capable of imaging the coronary arteries but the spatial resolution is currently lagging some way short of that capable with CTCA. Ozgun [77] performed a study comparing MRA with 16 slice CTA and MRA was found to have markedly worse specificity (62%) and sensitivity (82%) than the now surpassed 16 slice CT technology. A review of 28 MR coronary angiography studies including 903 patients shows 83% segments assessable and gave a sensitivity of 72% and specificity of 87%.[78] MR is more useful clinically in demonstrating cardiac function and viability and is also starting to play an important role in perfusion imaging.

1.5.d.ii Radionuclide perfusion imaging

Often used as a gateway to invasive coronary angiography, isotope perfusion scans give a similar radiation dose to CTCA. They provide information about coronary flow insufficiency which is fundamentally different to the anatomical information available from CTCA. Perfusion imaging is better placed at demonstrating the significance of coronary lesions whereas CTCA gives information on coronary artery plaque and stenoses even before they become flow limiting.

1.5.d.iii Stress echocardiography

This technique has similar sensitivity and specificity to radionuclide perfusion imaging and is used extensively in the UK due to the lack of ionising radiation. However it is fundamentally different to CTCA giving functional rather than the primarily anatomic data of CTCA. Its main limiting feature is poor image quality from subjects with unhelpful body habitus, although the use of transpulmonary contrast agents makes it possible to achieve acceptable diagnostic images in the majority of patients.

1.5.e The future

CT technology is continuing to develop rapidly with several major areas of advancement.

1.5.e.iDual-source CT

Dual-source CT offers substantial improvements in temporal resolution that are paramount in cardiac imaging. This is likely to see widespread uptake and further developments in multi-source CT are likely.

1.5.e.ii Increased number of slices

Scanners with larger arrays with more slices (eg 320-slice) allow a greater volume to be covered in one rotation of the scanner, thus reducing the breath hold and number of cardiac cycles over which a scan is performed. If the whole heart can be imaged in one cardiac cycle, prospective cardiac gating could be used more reliably, and this could lead to lowering of radiation doses, however this has not yet been delivered by current prototypes.[79] Whilst 256 and 320 slice scanners increase coverage, and reduce stitch artefact and decrease overall scan time, higher temporal resolution is still required to overcome motion artefact. All major manufacturers now have scanners above 64 slices with 128, 256 and 320 slices; the 256 slice scanner is reported to have a rotation speed of 250ms and thus a temporal resolution of 125ms, which represents an improvement over previous source scanners, but remains worse than that achievable with dual source scanners or invasive coronary angiography.

1.5.e.iii Increased spatial resolution and reduced noise

Improvements in detector technology that result in improved spatial resolution may allow the lumen of calcified or stented vessels to be better imaged, more sensitive detectors may improve image noise and allow for reduced radiation dose.

1.5.e.iv Flat panel detectors

Flat panel detectors offer very high spatial resolution, and can be considered an extreme example of increasing slice numbers thus increasing coverage and reducing detector unit width. Unfortunately the scintillator material used in flat panels is slower to respond to x-ray stimulation than that used in CT scanners and thus prolonged afterglow reduces the ability to deliver sufficient temporal resolution for cardiac CT applications and this will probably require the development of new

materials for flat panel detectors.[80, 81] They also have a lower contrast resolution. Whilst not applied to flat panel technology, one manufacturer, GE, have recently developed a new transparent polycrystalline scintillator material that makes a further leap in this direction. Although the new scintillator material has not delivered higher spatial resolution it is the speed of reaction of the crystal that is important. This new scintillator material has a primary speed one hundred times faster than the gadolinium oxysulfide scintillator (GOS) that is used by other manufacturers and an afterglow that is four times quicker to decay than GOS scintillators. GE have used this highly responsive scintillator to allow dual energy scans within one half rotation with one detector and x-ray source by employing rapid KV switching within a scan.[82] There is thus hope that new scintillators can also be developed for flat panel detectors.

1.5.e.v Dual energy

Not to be confused with dual source, dual energy is the technique whereby a single area of interest is scanned using x-rays generated at different voltages (kV) and hence different powers. As tissues interact differently with the different X-ray energies, the technique can help to improve tissue differentiation. In cardiac applications, it has the potential to 'remove' calcification, thus permitting a clearer view of the lumen. The technique is most elegantly performed using a dual source scanner or rapid kV switching, especially for cardiac applications when the use of a single source scanner would otherwise result in too poor a temporal resolution.

1.5.e.vi Iterative reconstruction

Iterative reconstruction is a repeated algebraic process by which an image is reconstructed from the linear data received by the scanner. It is in fact an old technique, but due to it's large demands for computational power it was replaced with filtered back projection (FBP) as the technique most widely deployed in CT image reconstruction. FBP as a technique produces quite noisy images and thus higher x-ray doses are required to overcome this. As computational power has greatly decreased in size, power and cost, the iterative process is being revisited. It is not purely the computational power that has become available but also the development of

mathematical models that improve the efficiency of the process by incorporating additional steps and assumptions. Sophisticated mathematical models that incorporate a building block created from a filtered back projection that is then refined using the iterative process, combined with mathematical representations of scanner geometry, have been developed that produce considerable reductions in image noise and artefact. These improvements allow imaging with lower x-ray doses and improve image quality, particularly in obese patients and in calcified vessels, or potentially in stents.[83-86] Computational power has continually increased and it's cost diminished over the last 50 years and it is likely that this trend will continue. In this context, iterative reconstruction is likely to take a greater role in clinical imaging technologies, including but far from limited to Cardiac CT angiography. Indeed all the cardiac CT scanner manufacturers have released implementations of such a technique.[87]

These and other technological developments will have significant impact on the accuracy and reliability of CT technology for assessing coronary artery disease and, if combined with the expected reduction in patient dose, the range of accepted clinical applications will expand.

1.5.f Applications of cardiac CT

1.5.f.i Calcium scoring

The evaluation and quantification of coronary artery calcium was one of the first cardiac applications of CT technology. Since the seminal work by Agatston,[17] a large amount of data have been collected in a variety of populations that demonstrate that the calcium score is a predictor of future cardiac events. [88, 89] Calcium scores were originally assessed by electron beam CT but it has now been shown that they can be accurately obtained by the increasingly available multidetector CT scanners. Calcium scoring is a non-contrast scan that uses a very low radiation dose and calcium scores can be quickly and automatically calculated. Given the increasing ability of CT to assess non calcified plaque and assess luminal narrowing it is clear there is potential for

obtaining further prognostic information from CTCA, however at present this requires a higher dose of radiation and the injection of intravenous contrast media. Kwon[90] demonstrated that CTCA was a better predictor of risk in a group of low risk patients.

1.5.f.ii Assessing native coronary artery disease

The technological advances that have occurred in cardiac CT have been directed towards non-invasive coronary angiography. The sensitivity and specificity of earlier 4-slice scanners to identify stenosed coronary arteries was such that this modality was not clinically useful. There have been, however, many studies comparing both 16-slice[91-102] and 64-slice[103-113] scanners with invasive quantitative coronary angiography. In terms of the studies with 64-slice scanners, most subjects have been male and nearly all have had stable, chronic angina although evidence is starting to appear from other groups such as acute chest pain.[114] Table 4 summarises some of the published studies investigating 64 slice CT for native coronary artery disease.

Table 4 64-Slice CT studies assessing native coronary arteries

Study	No. Patients	Excluded segments	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Leschka et al [103]	67	<1.5mm	94	97	87	99
Leber et al [104]	59	0	79	97	72	98
Raff et al [105]	70	0	86	95	66	98
Mollet et al [106]	51	0	99	95	76	100
Pugliese et al [107]	35	0	99	96	78	99
Malagutti et al [108]	55	0	97	86	66	99
Fine et al [109]	66	<1.5mm	95	96	97	92
Ropers et al [110]	81	<1.5mm	93	97	56	100
Plass et al [111]	50	<1.5mm	93	97	91	98
Ehara et al [112]	69	0	90	94	89	95
Schuijf et al [113]	60	0	85	98	82	99

It should be noted that all these studies, with the exception of the multi-centre study of older 16-slice MSCT by Garcia et al that showed markedly lower specificity[102], are single centre studies. The results above are generally based on a per segment or per

artery analysis of only the vessels that were of sufficient image quality on MSCT to be assessed and compare the ability to detect >50% stenoses. A meta-analysis[115], showed a sensitivity of 87% and specificity of 96% for 64-slice scanners.

Meijboom[116] assessed 360 patients referred for invasive coronary angiography. In a segment-based analysis, the sensitivity was 88%, specificity was 90%, positive predictive value was low at 47% , and negative predictive value was 99%.

Budoff[117] also undertook a multicentre study of 64 slice CT in 230 individuals. Using a vessel based assessment comparing stenosis ≥50% with invasive coronary angiography sensitivity was 84%, specificity was 90% and NPV was 99%, but PPV was only 51%.

The multi-centre study investigating 64 slice CT in native coronary artery compared with invasive coronary angiography CORE 64[118] only reported patient based results with similar results whether using quantitative CTA or visual lesion assessment. The value in reporting per-patient results is of questionable value and probably overestimates accuracy.

The sensitivity and specificity of 64-slice scanners is greater than that of the 16-slice scanners. In addition the studies investigating 64-slice scanners rarely excluded coronary artery segments on the basis of size, whereas this has been done frequently with the 16-slice scanners.

Evidence from dual source CT and larger 256 and 320 slice scanners are starting to show smilar accuracy when compared with 64 slice CT.[119-121]

1.5.f.iii Assessing grafts

Saphenous vein grafts are easier to image with CT, being generally larger than coronary arteries and less mobile. Invasive coronary angiography, on the other hand, can be technically more challenging in such patients, with larger contrast loads and radiation exposure. Native coronary arteries in these patients often become heavily calcified making interpretation of stenoses difficult. Studies assessing the accuracy of CT in this group of patients are summarised in Table 5. Again, the sensitivity and specificity of 64-slice scanners is greater. Volume rendered images can also be useful when planning re-do bypass grafting.

Table 5 Studies investigating coronary graft assessment by CTCA

Study	Slices	No. patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Schlosser et al [122]	16	48	96	95	81	99
Burgstahle et al [123]	16	13	100	96	89	100
Anders et al [124]	16	32	80	85	57	94
Stauder et al [125]	16	20	98	95	93	98
Pache et al [126]	64	31	98	89	90	98
Malagutti et al [108]	64	52	99	96	95	99
Ropers et al [127]	64	50	100	94	92	100

1.5.f.iv Assesment of LV function

As data are collected throughout the cardiac cycle, movie images of the heart throughout the cardiac cycle can be made demonstrating regional wall motion abnormalities. Comparison of systolic and diastolic volumes allows accurate assessment of stroke volume and ejection fraction.[128, 129] This technique cannot be used with prospectively gated scans were images are only obtained during part of the cardiac cycle.

1.5.f.v Defining pulmonary vein anatomy

CT is also becoming more widely used during electrophysiological procedures, in particular atrial fibrillation (AF) ablation. A 3D CT image of the atria can be superimposed on the electrophysiology map improving the ability to localise pulmonary veins and reducing fluoroscopy times.[130]

1.5.f.vi Evaluating morphology

MSCT can also be used to identify the course of anomalous coronary arteries (Fig 13), which may be important where they take a so-called “malignant” course in between the aorta and pulmonary trunk,[131] and to assess complex congenital heart disease.

1.5.f.vii Evaluating structural lesions

Cardiac masses, thrombus, pericardial, pulmonary and aortic pathology are well delineated by cardiac CT.

1.5.f.viii Plaque characterisation

In contrast to conventional coronary angiography, CT has the potential to look at the coronary artery wall in addition to the lumen. Whilst not clinically useful currently, it may become possible to identify non-calcified plaque that is not flow-limiting but which is "unstable" and may lead to an acute coronary syndrome (Figure 12). A technology that provides the potential to non-invasively assess the early stages of plaque formation and characterise its composition and prognosis has the potential to cause a huge shift in the practice of cardiology. Meta analysis of studies comparing recognition of plaque type when compared with IVUS has demonstrated sensitivity of 88-95% and specificity of 90-96%.[132]

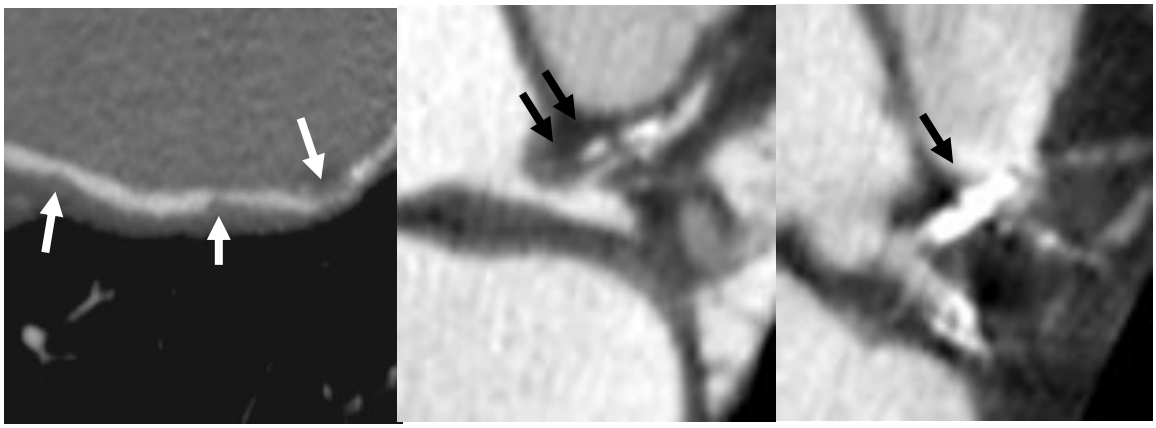


Figure 12 Plaque characterisation by CT. Three different plaque types are illustrated showing the darker appearance of soft plaque, the bright appearance of calcified plaque and mixed plaque with features of both.

1.5.f.ix Perfusion imaging

Whilst the pharmacokinetics of CT contrast agents will allow first pass perfusion imaging[133] and assessment of delayed enhancement (for scarred myocardium), MSCT is not widely used in this role – although there are on-going studies. The radiation doses involved remain a concern as this information can be obtained by cardiac

magnetic resonance imaging (CMR), which does not use ionising radiation. However with the increasing implantation of pacing and resynchronisation devices generally rendering cardiac MRI unsafe, there may be a role in a small number of patients.

1.5.f.x Assessment of coronary stents

Coronary stents pose difficulties for imaging by CTCA due to their size and the density of the material from which they are constructed causing artefacts. With 16 slice scanners, the results suggest the technique is not sufficiently reliable for clinical use. There is not yet sufficient clinical data with 64 slice scanners to see if the improved technology has led to improved reliability in this group. This will be extensively explored in chapter 5.

1.6 Circulating biomarkers in coronary artery disease

Circulating biomarkers are substances involved in disease biology that are amenable to measurement and evaluation and provide information about the underlying disease process in terms of diagnosis, severity or prognosis. A huge array of biomarkers of cardiovascular disease are at varying stages of assessment, a number of which have fulfilled their translational potential and found major clinical application (table 6).[134, 135] This is particularly true of troponins and natriuretic peptides which now play a central role in the diagnosis of myocardial infarction and heart failure. There is also evidence that these novel biomarkers may have a role for risk stratifying patients with stable coronary disease. Their diagnostic potential in patients with suspected angina attending chest pain clinics will be explored in more detail in chapter 6.

Table 6 Biomarkers in cardiovascular disease

- **Accelerated atherosclerosis**- HBA1c, Blood glucose, lipid profile
- **Inflammation** – HS CRP, myelpoeroxidase
- **Vascular damage** –CrCL, microalbuminuria
- **Myocyte injury** –CK, CK-MB, cardiac troponin I and T, GDF-15
- **Haemodynamic stress** –BNP, NT-Pro-BNP, copeptin

1.6.a Cardiac troponins

The evaluation of myocardial infarction using biomarkers is now so embedded in our clinical practice that the definition of myocardial infarction includes elevation of biomarkers as one of its key tenets.[136] However it was only with the development of assays for CK and CK-MB[137] in the last 50 years that this concept was first included in the generally accepted definition of myocardial infarction. [138] Since then the definition has been further elaborated and refined[139] but the importance of cardiac biomarkers remains paramount.

Initially CK-MB was the main cardiac biomarker used in the diagnosis of myocardial infarction but since the 1990s it has been shown that cardiac troponins I and T are sensitive and specific markers of myocardial injury[140] and have now largely superseded the earlier use of the less specific biomarkers such as creatine kinase.[141]

In contemporary clinical practice it is the cardiac troponin subunits Troponin I (TnI) and Troponin T (TnT) that are ubiquitously used in the setting of myocardial infarction. These troponin subunits are part of the thin filaments in cardiac and skeletal muscle and in combination with a third subunit, troponin C form part of the cardiac troponin regulatory proteins.

For muscle contraction to occur intracellular calcium ions are released from the sarcoplasmic reticulum and bind to Troponin C, resulting in a conformational change in the complex with tropomyosin, withdrawing troponin I from the myosin binding site on actin, and allowing the myosin of the thick filaments to bind. Conformational change of the myosin head unit, fuelled through the hydrolysis of ATP causes the thick

filament and thin filament to slide in relation to each other and muscle contraction occurs.

The majority of troponin subunits are bound in sarcomeres, whereas the remainder are free in the cytoplasm. For cTnI this free pool appears to represent 3-4% of cellular cTnI and 6-8% for cTNT.[142, 143]

Troponin subunits I and T have cardiac specific isoforms, whereas troponin C has shared isoforms with skeletal muscle. Cardiac troponins are released into the systemic circulation when cardiac myocytes are subject to injury and undergo necrosis. Thus cardiac troponin I (cTnI) and cardiac troponin T (cTnT) have been logical targets as biomarkers for assessing damage to myocardial cells.

Both cardiac cTnT and cTnI have been shown to be specific and sensitive markers for the diagnosis of myocardial infarction and levels also exhibit prognostic utility.[144, 145] In the setting of myocardial infarction this is in keeping with the fact that the greater amount of myocardial infarction and thus myocyte necrosis, the greater the release of cardiac troponins. As more of the myocardium is infarcted the degree of left ventricular dysfunction increases leading to heart failure and a larger substrate for the development of potentially fatal arrhythmias.[146]

1.6.a.i Troponin elevation in absence of coronary occlusion

It has however been noted that elevation in cardiac troponin levels is not purely found in the setting of myocardial infarction but may also occur in a range of other pathologies.[144, 147]

Table 7 Non - coronary causes of elevated troponin

- Acute heart failure
- Pulmonary embolism
- Stroke
- Acute aortic dissection
- Tachyarrhythmias
- Hypotension / Shock
- Sepsis
- ARDS
- Perimyocarditis
- Endocarditis
- Tako-tsubo cardiomyopathy
- Radiofrequency catheter ablation
- Cardiac contusion
- Strenuous exercise
- Sympathomimetic drugs
- Chemotherapy

The mechanism for this elevation in troponin levels in the non myocardial infarction setting is debated. In some disease states such as pulmonary embolism and myocarditis myocardial injury could still be occurring. Although not due to coronary occlusion, this could lead to cell necrosis and troponin release. However this theory does not fit well in situations such as stroke and sepsis, where it is harder to develop a model for myocardial necrosis.

It is also now well documented that rises in cardiac troponins can occur in a large proportion (nearly 50%) of healthy individuals undergoing extreme exertion such as marathon running and this has been demonstrated in a variety of athletes including adolescents. It has been noted that the release of troponin in this context has a different profile to that occurring in myocardial infarction, with a shorter decay period returning to baseline quicker.[148] Thus one must consider the possibility of an alternate

mechanism of release for troponin outwith the setting of mycocyte necrosis. Katus [149] also noted differing release kinetics between those patients suffering myocardial infarction but undergoing early reperfusion and those not. Muller-Bardoff[150] demonstrated that patients with pulmonary embolism had a cTnT release that decreased faster than in patients with acute coronary syndrome, again suggesting there may be a different underlying mechanism.

One possible explanation for the elevated levels of troponin I and T and delayed clearance in patients with renal impairment [151] is that there is always a small quantity of troponin in the circulation and that when this is allowed to accumulated due to reduced clearance, it becomes detectable with current assays. If this is not the case a mechanism either of recurrent small myocardial infarction or some other loss of membrane integrity must be the cause of the raised levels of troponin identified in patients with end stage renal failure.[152]

1.6.a.ii Mechanistic theories for troponin release in absence of coronary occlusion

With that in mind we must consider the possibility that troponin release does not solely occur due to cell necrosis. The two hypotheses that have developed to explain the observation of elevated troponin in the absence of overt myocardial infarction are the 'minor irreversible damage' theory and 'cytosolic leak' model.

Minor irreversible damage is the theory that small levels of cardiac necrosis occur in all these disease states, sufficient to release detectable troponin, but insufficient to cause detectable levels of myocardial necrosis or its sequelae by means of imaging or clinical assessment. The concept of cytosolic leak is that pathological, or indeed extremes of physiological states can lead to leakage of small levels of cardiac troponin into the circulation from cells which are not undergoing necrosis and thus there is no irreversible myocardial damage occurring.

1.6.a.iii Troponin release and imaging evidence of infarction

In the setting of small troponin rises in response to extreme exercise, various imaging and clinical assessments have generally shown no evidence of myocardial scar.[153]

Although one study by Niemala[154] showed evidence of LV impairment in response to extreme exertion as assessed by echocardiography. The concern however is that the amount of myocardial infarction may be too small to be detected by such means. Indeed it has been shown that in acute coronary syndromes or after PCI, despite significant troponin release, presumed due to myocardial necrosis this may not be detectable by clinical, echocardiographic, nuclear or magnetic resonance imaging techniques.[155, 156] Thus it cannot be affirmed that the presumably small amount of necrosis in the minor irreversible damage theory would indeed be detectable by any current modalities having a comparatively low spatial resolution, and this alone is insufficient evidence to refute the minor irreversible damage theory.

1.6.a.iv Release kinetics and mechanistic theories

The comparison of the release kinetics of troponins in myocardial infarction is also inadequate evidence to support the cytosolic leak theory. In myocardial infarction there are many confounding factors that may alter the release profile of troponins. Microvascular obstruction is a well recognised phenomenon[157] and this could contribute to the slower sustained release of troponin compared with non-infarct release. The observation that the release of CK is much faster and quickly falls to baseline in myocardial infarction would tend to counter this argument, as CK is likely to be affected in a similar way to troponin by microvascular obstruction. The relative size of the CK and troponin molecules does not easily explain the differing release profiles. CK 86000 daltons (half for each subunit) troponin I 28000, troponin T 41000 and troponin C 18000 daltons.

The measured CK-MB is largely cytoplasmic, and not a measure of mitochondrial or sarcoplasmic CK whereas the majority of troponin I and T is bound in the sarcoplasm. If we were measuring purely the cytoplasmic troponin we may expect a similar release profile, however in cell necrosis both the cytoplasmic and sarcoplasmic troponins are released. It has been suggested that the prolonged troponin release profile in myocardial infarction represents the release of the small proportion of troponin which is cytoplasmic followed by a slower release of the majority of the troponin that is found within the sarcomeres. Thus this does support the concept that a faster release

and decay of troponin in non-infarct settings may reflect the release of only the cytosolic troponin due to membrane leak. This would explain the similarity between the CK release profiles in myocardial infarction and the release profiles of troponin in non-infarct disease states.

1.6.a.v Cell membrane disruption and troponin release

Animal studies help to build support for the model of cytosolic leak by investigating the causes and consequence of cell membrane disruption or permeability. Remppis[158] exposed isolated rat hearts to a calcium paradox to cause cell membrane damage. The cells exhibited faster onset and return to baseline of troponin release compared to a no flow ischaemia model in a similar manner to the earlier described rapid rise and fall of troponin in endurance athletes.[148]

Remppis induced cell membrane disruption using a chemical technique but demonstrated that this led to troponin release, most likely from the cytosolic pool, however evidence that mechanical stress and exercise can induce cell membrane permeability is also required to support the cytosolic release theory. Clarke[159] demonstrated that cardiac myocytes could undergo survivable cell membrane wounding in response to mechanical stress and that this was exacerbated by β-adrenergic stimulation of heart rate and force of contraction. McNeil[160] demonstrated exercise induced membrane wounds in rat skeletal muscle. It is known that the heart adapts by undergoing hypertrophy of myocardium in certain situations of increased load such as hypertension and severe aortic stenosis. Myocytes undergoing this process exhibit an elevated rate of contractile protein synthesis. Stretching rat cardiac myocytes isolated on a deformable material[161] results in rapid induction of genes and multiple messenger pathways. Fischer[162] demonstrated transient cell membrane permeability in response to abrupt pressure loading of rat hearts.

Thus we have seen that there is some evidence supporting the theory of cytosolic leak, that membrane permeability can be induced by mechanical stress and that membrane permeability leads to release of troponin with kinetics similar to that seen in disease states without coronary occlusion.

1.6.a.vi Troponin release in response to acute ischaemia

Chocron demonstrated that myocardial ischaemia was associated with the release of cardiac troponin I in isolated rat hearts with no significant histologic difference between the group with shorter ischaemic time and controls, despite having raised troponin levels.[163] A caution here that the sample size was small and the shortest ischaemic time was three hours.

An elegant study by Suleiman demonstrated release of troponin I into the coronary sinus of patients undergoing off-pump CABG after only 3 minutes of controlled regional ischaemia.[164]

Feng used a pig model whereby flow in the LAD was reduced by 36% and cTnI raised in reversible ischaemia compared with controls.[165] Chen[166] demonstrated that rats forced to swim had increased troponin T (and evidence of inflammation) in serum and myocardium compared with controls and had histological evidence of damaged myocardial fibres and inflammatory infiltrates rather than necrosis.

Thus we have seen a plausible mechanism for the release of troponin in patients without coronary occlusion, and evidence that both mechanical and ischaemic factors can lead to cell membrane permeability and that transient ischaemia leads to troponin release.

An interesting exception to the model of cytosolic leak in the reversible ischaemia model was noted by Tung in the case of subarachnoid haemorrhage where troponin elevation was associated with histologically demonstrated myocyte necrosis, probably neurally mediated.[167]

The above works do support the hypothesis of a cytosolic membrane leak as a source of elevations in circulating troponins in reponse to ischaemia, however the evidence is considerably muddied by the variety of troponin assays used and the inherent errors and limits of detection. It is necessary in the current era of higher sensitivity assays to repeat some of this work to enable a better understanding of the role and mechanism of elevated cardiac troponin levels in the non-infarct setting.

1.6.a.vii Troponin elevation in stable coronary artery disease

Looking now to clinical studies of troponin in patients with stable ischaemia the evidence is less encouraging. Troponin measurements are well established in the diagnosis of acute coronary syndromes, however their role in the assessment of stable angina is less clear. In stable coronary artery disease, multiple micro-infarcts, similar to the proposed minor irreversible damage theory could lead to troponin release, or via some mechanism leading to cytosolic release such as during periods of ischaemia as discussed above. All these studies were performed with older, less sensitive assays than I will use later in Chapter 6.

Angioscopy studies have demonstrated the presence of plaque rupture and thrombosis in stable angina patients.[168] Mann[169] demonstrated that 22% of histopatholgical specimens examined in patients with stable angina had evidence of thrombus formation. Using optical coherence tomography 12% of patients with stable angina had disrupted plaques and 35% had thrombus formation.[170] Mann[171] demonstrated from necropsy specimens that coronary arteries appear to undergo a phasic pattern of atherosclerotic plaque progression with continual rupture and healing, if these plaque ruptures lead to micro-infarction one would expect some release of troponin, that may be detectable in these patients.

Carlson[172] studied patients with evidence of ischaemia on dobutamine stress echo and showed that they had no difference in baseline troponin I or T levels and no rise in troponin from baseline after stress compared with those with no evidence of ischaemia. Thayapran[173] demonstrated no increased troponin I or T in any patients before or after exercise despite evidence of ischaemia on perfusion scan.

Kokowicz[174] did demonstrate a rise in troponin I levels after exercise in a small group of patients but this did not correlate with the number of stenotic lesions on invasive coronary angiography nor did it correlate with prognosis. It was however noted more commonly in patients with impaired left ventricles or high systolic exertional blood pressures, perhaps a surrogate for LV wall stress.

Eggers found elevated troponin I levels in 22% of a population over 70 years old and this correlated with LV impairment and LV hypertrophy but not the presence of scar by MRI. [175]

In a sample of the Dallas population raised troponin T ≥0.01µg/L was found in only 0.7% of the population aged 30-65 and demonstrated an association between elevated troponin and LVH, CKD and a composite heart failure index.[176]

In a group of 70 year old men in Sweden with no clinical evidence of current or prior coronary artery disease, cTnI ≥0.04µg/L was associated with first cardiovascular event and mortality.

It is difficult to combine the data from these various studies to get a clear understanding, as most of the biomarker elevations seen, particularly with the troponins, are at the lower end of the assays' detectable limits, and as the assays are refined the limit of detection becomes lower and the accuracy of measurements at these lower limits becomes more reliable.

Since my research was commenced there have now been even more sensitive assays developed that detect troponin I in nearly all healthy subjects.[177] Thus the concept that any level of detectable troponin must represent myocardial necrosis cannot be correct. With this knowledge and the evidence from the animal studies and human studies described above, the model of a continual slow turnover and elimination of troponin from the circulation is likely to represent physiological normality. And it is plausible that disruption of this balance by processes such as the cytosolic leak theory can give rise to higher levels of troponin, and it is clearly necessary to examine the levels, profiles, mechanisms and consequences of the elevations found in these differing disease states.

1.6.b Brain Natriuretic Peptide (BNP)

The measurement of the neurohormone BNP has become an important diagnostic tool in the evaluation of heart failure. It was originally isolated from porcine brain and thus given the name brain natriuretic peptide, but it is present in greater concentrations in

myocardium in response to cardiac stress and is now generally called B-type natriuretic peptide or simply BNP. In humans three natriuretic peptides are recognised; atrial natriuretic peptide (ANP), BNP and C-type natriuretic peptide (CNP) which is largely produced outside the heart.[178] A fourth natriuretic peptide; dendroaspis natriuretic peptide (DNP), first isolated in green mamba venom may be a fourth endogenous natriuretic petide, though the evidence is as yet is inconclusive.[179]

BNP is released in response to left ventricular wall stretch and volume overload. Its elevation in the plasma is a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. BNP is also elevated in end stage renal failure and valvular heart disease.[180] Along with the other cardiac natriuretic peptides, BNP plays a role in maintaining the compensatory mechanisms that are present in heart failure by promoting natriuresis, diuresis and vasodilation. Although small quantities of BNP are stored in the atria, BNP is not stored in significant quantities in cardiac ventricular myocytes and its transcription is upregulated in response to cardiac stress as discussed above.[181] When BNP is secreted it is cleaved from a pre-prohormone into the prohormone proBNP which is further cleaved into the active component BNP and the inactive fragment N-terminal proBNP (NT-proBNP). BNP is cleared by binding with the inactive natriuretic peptide receptor - C and neutral endopeptidase (NEP) and a small proportion (<5%) is cleared renally with a half life of approximately 20 minutes.[182, 183] NT-proBNP is also cleared renally but at a slower rate with a half life thought to be 27-120mins.[184] In healthy individuals there are very small levels of ANP and BNP produced in the atria. However in disease states, the ventricles produce large quantities of BNP, compared with a relatively modest change in ANP levels.[185] It is this large difference between healthy and disease states that is a key factor in the clinical application of BNP as a useful biomarker.

BNP binds to the cGMP coupled receptor natriuretic peptide receptor A (NRP-A) which is found in adrenal, lung, renal, adipose, ileal and aortic tissue.[186] In human subjects infusion of synthetic BNP caused natriuresis and diuresis and suppressed plasma aldosterone.[183] Mice with overexpression of BNP have hypotension and bone adbnormalities whereas BNP knockout mice developed multifocal cardiac fibrosis but

not hypertension. This has led to the suggestion that BNP may also exert a paracrine effect, potentially acting upon cardiac fibroblasts. [187, 188]

1.6.b.i BNP elevation in models of ischaemia

Although the main stimulus for BNP is increased ventricular pressure and volume, it may also be secreted in response to myocardial ischaemia independent of ventricular pressure changes.[189] In animal models Toth[190] demonstrated that hypoxia increases circulating BNP in isolated rat myocardium, despite a decrease in LV pressure. Similar results were obtained by D'Souza in ischaemic rat hearts.[191] Hama ligated a coronary artery inducing infarction rather than ischaemia in rats and showed an increase in ventricular myocardial BNP and BNP mrNA.[192] Goetze demonstrated increased BNP mRNA in ischaemic pig myocardium compared with non-ischaemic areas in the same hearts, further helping to exclude ventricular stretch as the stimulus, although the possibility of regional wall stress triggering BNP production remains. In the same paper it was also demonstrated that BNP mRNA was increased in oxygen deprived myocytes in culture medium.[193]

Patients undergoing CABG or PCI but with normal LV function all had higher BNP and NT-proBNP than controls. Ventricular BNP mRNA expression in biopsies taken from hypoxic areas of myocardium in the CABG group correlated with plasma BNP and plasma NT-proBNP.[194] Even transient ischaemia due to balloon inflation during coronary angioplasty can produce elevation of BNP.[195]

1.6.b.ii BNP changes on exertion

Given the evidence that BNP is released in response to ventricular stretch it is likely that it may rise in response to the haemodynamic load of exertion. Indeed all endurance athletes in a study by Neumayr had a measureable rise in NT-proBNP in response to extreme and prolonged exertion.[196] Kohno measured the coronary sinus plasma levels of BNP in a group of hypertensive patients and noted increased BNP on ergometric exercise that was reduced by administration of an ACE inhibitor.[197] The development of regional wall motion abnormalities during exercise or stress in

patients with coronary artery disease inducing regional ischaemia is the basis of the stress echo assessment of ischaemia and is a well established phenomenon. The development of such regional variations in myocardial contraction may produce areas of increased wall stress within the ventricle that could trigger BNP release to a greater extent in such patients compared with patients with more global co-ordinated contraction.

Studies assessing BNP changes in the setting of ischaemia are largely conflicting and will be examined below. There are several studies demonstrating that the rise in BNP or NT-proBNP on exertion is greater in the presence of ischaemia. Further studies suggest that the increase is largely associated with LV dysfunction, raised LV end diastolic pressure or areas of scar which may also be related to LV impairment. A final group of studies suggest that it is the baseline BNP that is of significance and not the change on exercise.

Marumoto demonstrated increased BNP levels on exercise in 35 individuals with angiographically proven coronary disease and stable angina compared with no elevation in a normal control subjects, whereas ANP rose in both groups.[198] In the study by Chatha, NT-proBNP increased in patients with exercise ECG evidence of ischaemia but didn't increase more than those without.[199]

Foote found that patients with known CAD, normal LV function, ischaemia on perfusion scanning and normal resting BNP and NT-proBNP had post exercise BNP higher than those patients with coronary disease but no evidence of ischaemia and healthy volunteers.[200] However they were surprised to note that the baseline NT-proBNP and BNP were also significantly different between the two groups.

Although they did not look at the association between ischaemia and BNP Marumoto demonstrated that increased BNP on exercise in patients with proven prior myocardial infarction correlated with LV function and LVEDP.[201] Similarly Palumbo investigated patients with fixed, reversible or no perfusion defects on SPECT scans and noted that the highest levels of BNP was found in those with fixed defects, however those with reversible perfusion defects had higher levels than those without perfusion defects.[202]

Thus BNP does appear to rise in response to ischaemia but the degree to which the extent of change is directly related to ischaemia is unclear.

1.6.b.iii Baseline BNP in patients with ischaemia

The studies by Weber,[203] Yeo[204] and Asada[205] suggest that it is the baseline BNP that is more useful as a predictor of ischaemia than the change in BNP on exertion. Weber[203] found that NT-proBNP levels were raised in patients with CAD demonstrated on coronary angiography or with ischaemia and the ischaemia extent by SPECT correlated with NT-proBNP level. However they documented no increase on exercise at 15 minutes. Yeo[204] examined patients with coronary artery disease. Those with ischaemia on SPECT had higher baseline BNP and NT-proBNP than non ischaemic or healthy volunteers, but also demonstrated a higher rise in ischaemic than non-ischaemic group after exercise, even when fixed defects representing prior infarct were excluded from the comparison. Asada,[205] in a group of patients with known or suspected CAD found that pre- dobutamine stress echo (DSE) BNP levels predicted ischaemia but that the change between pre and post DSE was not significant. Bibbins-domingo[189] assessed 355 patients with either clinical, angiographic or scintigraphy evidence of ischaemic heart disease or prior myocardial infarction. It was found that baseline BNP level was associated with inducible ischaemia on exercise echocardiography.

There is a clear difference in the level of exertion undertaken by the endurance cyclists in Neumayrs study[196] and the intensity and duration of exercise in the other studies in clinical settings. It may be that the release of BNP requires a longer sustained period of exertion that many of my subjects, particularly those with limiting angina will not be able to achieve. A large part of the observed elevation of BNP particularly at rest could be related to ventricular pressure changes related to even small areas of LV impairment, however it is interesting to see that even when taking this into account there does seem to be a trend for patients with ischaemia demonstrating higher levels of BNP at rest.

1.6.b.iv BNP as a predictor of cardiovascular events

BNP has important prognostic value in unstable coronary artery disease. In acute coronary syndromes, levels of BNP and N-terminal pro-brain natriuretic peptide (NT-proBNP) strongly predict mortality and risk of future heart failure, independent of known risk factors.[206] The usefulness of these cardiac peptides in identifying unstable patients with significant coronary stenoses extends to those with normal ECGs, echocardiograms and cardiac enzymes. [207] NT-proBNP predicted later LV dilatation post STEMI.[207] NT-proBNP increased in unstable angina but not stable angina.[208]

Emerging evidence suggests that BNP is related to prognosis even in patients with stable coronary disease. In the study of Omland et al. 186 patients with angiographically proven stable coronary disease were followed up for a period of 7.4 years. Plasma BNP levels were independently related to long term survival.[209]

Ndrepepa and Kragelund showed an association between degree of coronary artery disease and baseline NT-proBNP and BNP levels. Ndrepepa [210] found that NT-proBNP predicted mortality in 1059 stable angina patients with angiographically demonstrated coronary stenoses but no detectable troponin rise who subsequently underwent percutaneous coronary intervention. Kragelund[211] demonstrated that in stable subjects with angiographically proven coronary disease, higher NT-proBNP levels were seen with greater degrees of coronary disease irrespective of LV ejection fraction by LV gram and LV end diastolic pressure (LVEDP) and NT-proBNP was a prognostic marker of all cause mortality.

Bibbins-Domingo[212] studied 987 patients with previous MI, angiographic stenoses or evidence of ischaemia. Although they adjusted for LV function, the correlation between mortality and cardiovascular events was strongest in those with EF>50%. NT-proBNP did have weak association with future myocardial infarction but the greatest predictive value was for new onset heart failure.

In a wider selection of the general population BNP levels seem to predict mortality and heart failure but are not a strong predictor of coronary artery events. In Kistorp's cohort of people aged 50-89 NT-proBNP when adjusted for LVEF was predictive of first major cardiovascular event (stroke or heart failure) and death, but there was no link

with CHD events such as myocardial infarction.[213] Similar findings were obtained by Wang who measured BNP levels in the Framingham offspring study of unselected members of the community. Here BNP was most strongly associated with heart failure and atrial fibrillation with no link to coronary artery disease. However when they adjusted for LV function by echo the association between BNP and most outcomes was attenuated.[214]

Table 8 BNP and Ischaemia

- Ischaemic tissue has increased BNP or BNP mRNA (1.6.b.i)
- BNP increases in healthy subjects in response to extreme exertion (1.6.b.ii)
- Weak evidence that rise in BNP on exertion correlates with ischaemia (1.6.b.ii)
- Baseline BNP correlates with ischaemia (1.6.b.iii)
- Baseline BNP is poor predictor of myocardial infarction (1.6.b.iv)
- Baseline BNP predicts heart failure or surrogates (1.6.b.iv)

Thus raised BNP levels do appear to be predictive of mortality, stroke and heart failure but there is less evidence that it is predictive of coronary events such as myocardial infarction. Baseline BNP levels do appear to predict ischaemia but the significance of the response to exercise or stress is unclear.

1.7 Summary

In this introductory chapter the pathogenesis of coronary artery disease by atherosclerosis has been outlined and the importance of its sequelae discussed. It has been seen that PCI and coronary artery stenting play an important role in the treatment of coronary artery disease and techniques for assessing restenosis within coronary stents have been discussed. The technology underlying CT calcium scoring and CT coronary angiography has been explored in some depth and the evidence of its utility has been shown. In the following chapters aspects of the CTCA technique will be explored and evidence for its efficacy in assessing native coronary artery disease and in

stent restenosis against the gold standard of intravascular ultrasound will be sought. The evidence for the role of the biomarkers cardiac cTnI, cTNT and BNP in the diagnosis and prognosis of coronary artery disease in the acute but also in the chronic setting in stable patients has been examined. It has been shown that there is evidence from both animal, human and population studies suggesting evidence of release of both markers in chronic CAD and mechanistic models have been described.

Chapter 2 will outline the cohort of patients recruited to the various parts of my research and highlight some important considerations in these groups.

In Chapter 3 the effect of heart rate and rhythm will be explained and the medications available to reduce heart rate at the time of scan to improve image quality will be explored. A systematic review of the literature on CTCA will be undertaken to assess the rate control regimes in use. The rationale for the development of the rate control strategy employed in my centre will be discussed. This regime will then be assessed to try to gain some insight into its utility in clinical practice.

In Chapter 4 the ability of CTCA to assess native coronary artery disease will be explored, comparing the accuracy of the technique in this setting with that demonstrated in other studies.

In Chapter 5 the accuracy of 64 slice CT coronary angiography for in stent restenosis will be examined, along with a discussion of the particular challenges faced in assessing coronary artery stents. Establishing a more appropriate gold standard of IVUS for the assessment of in stent restenosis, comparision will be made between CTCA and invasive coronary.

Chapter 6 demonstrates the potential utility of CTCA as an endpoint in the assessment of coronary artery disease. I will explore the role of calcium scoring and CT coronary angiographically determined stenotic plaque and the biomarkers BNP and TnT, compared with exercise electrocardiogram testing in a cross-sectional study of patients attending a RACPC in North East London.

Chapter 7 summarises the findings of this work and looks to the future of CTCA.

2. COHORTS

Three groups of patients were the subject of my research.

Cohort 1, recruited from the outpatient service at the London Chest Hospital, is examined in Chapters 4 and 5.
Cohort 2, recruited from the Newham University Hospital RACPC is examined in Chapter 6.
Cohort 3 comprises 121 patients of whom 81 patients are from Cohort 1 and 40 patients from the Hospital of St John and St Elizabeth radiology department. This is the first group to be examined in the following chapter.

2.1 Cohort 1

The cohort examined in Chapters 4 and 5 represent a group of 80 patients all who had undergone previous coronary intervention and stent deployment. They were recruited after referral for invasive angiography for investigation of recurrent angina. All consented to additional CTCA64 and a subgroup to intravascular ultrasound (IVUS) for gold-standard assessment of stent restenosis.. This group differs from the patients assessed in many of the studies outlined in chapter 1 investigating the accuracy of CTCA which in the majority focused on patients with suspected coronary artery disease and represented a generally lower risk group. In contrast, cohort 1 had known coronary artery disease and prior coronary stenting. My use of IVUS for accurate assessment of restenosis meant that only patients with patent stents could be included in the diagnostic evaluation of CTCA64 within the stent component of the study. Patients with occluded stents were, of necessity, not available for analysis yet represent the group most readily diagnosed by CTCA64. Inevitably, therefore my use of IVUS as a gold standard set the bar very high for CTCA64.

2.2 Cohort 2

The cohort examined in chapter 6 comprised 229 patients recruited from a rapid access chest pain clinic in Newham in London. This RACPC was one of the earlier RACPCs in the UK, established in 1996 and in previous studies has been demonstrated to have a large proportion of non-white patients. This is reflected by data from the ONS in Figure 13 below which shows the high proportion of South Asians in the community.[215]

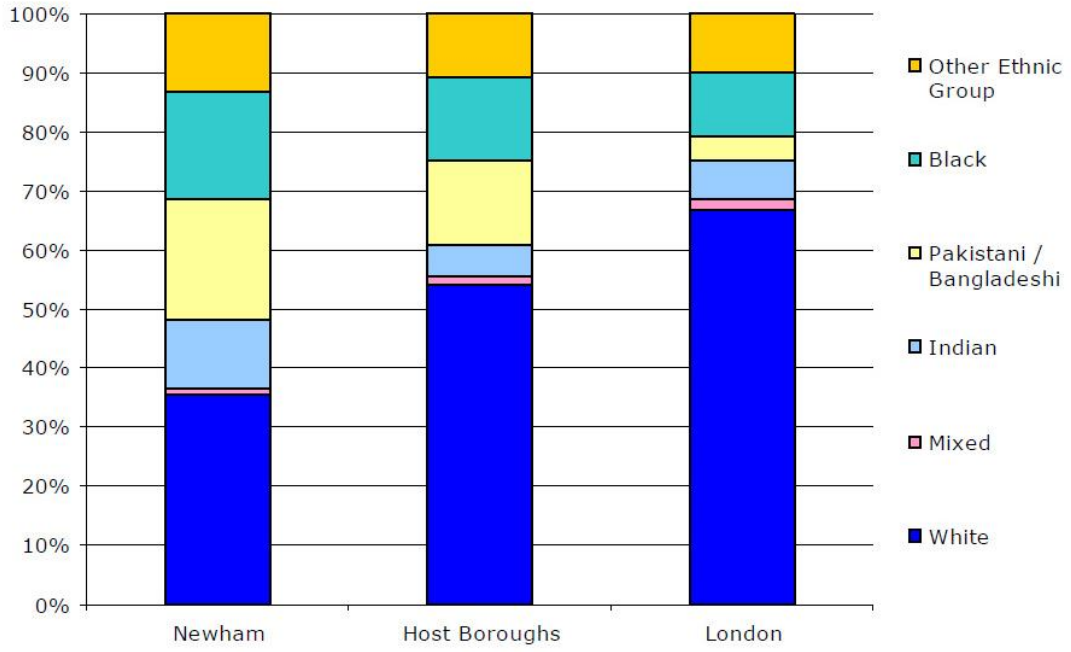


Figure 13 Newham population breakdown by ethnicity in 2007[215]

The table below is reproduced from unpublished work [216] and represents a larger cohort of patients investigated in earlier work from the same RACPC. In patients with both angina and non cardiac chest pain there is a high percentage of South Asian patients.

Table 9 Ethnicity in previous cohort recruited from Newham RACPC[216]

Diagnosis	Angina(25%)	NCCP (75%)
Ethnicity		
White	55%	40%
South Asian	38%	44%
Black	8%	16%
Risk factors		
HTN	51%	31%
Diabetes	24%	11%
Smoker	23%	23%

The importance of racial group in this context is that epidemiological studies have identified high levels of diabetes and coronary artery disease in south Asian patients.[217] Particularly pertinent to CTCA technology is the evidence that these patients have smaller coronary arteries.[218, 219] Assessment of small structures is limited by the available spatial resolution of CT technology. In CTCA the technology is operating close to its current limits of spatial resolution in assessing coronary arteries and thus a cohort with smaller vessels may be harder to assess.

The area served by the RACPC is one of the poorest areas in London with high rates of deprivation and poverty and with lower life expectancy than the London average.[215] In 2007 Newham was ranked as 4th most deprived in the United Kingdom.[220] Some of the limitations in the studies in chapter 6, to be discussed in more detail later, derived from the unwillingness of patients to re-attend for repeat blood tests or to travel for additional CT scans. It may be that the relative poverty of this study group influenced their ability to take the time to attend scans during the working day.

2.3 Cohort 3

In chapter 3 the importance of slow regular heart rates during CTCA will be examined and efficacy of a heart rate lowering regime in use in our institution will be explored.

The final cohort examined in this chapter comprises a total of 121 patients. 94 of these patients were recruited as part of research studies and 27 were undergoing CTCA at the Hospital of St John and St Elizabeth for clinical indications. The 94 patients recruited as part of research studies represent early recruits to cohorts 1 and 2, recruited according to the criteria for the studies documented in chapters 4-6. Thus the proportion of cohort 3 with coronary artery disease was appreciably larger than expected in the routine clinical setting and this is made clear from the data in chapter 3 with many of the subjects already treated with beta blockers at the time of CTCA. Patients with asthma were excluded from cohort 1 and this group is thus under-represented in cohort 3.

Table 10 Summary demographics and risk factors for Cohort 1-3

	COHORT 1 (n=80)	COHORT 2 (n=229)	COHORT 3 (n=121)
Demographics			
Age (years) Mean ±SD, Median (IQR)	63±10	53(11)	58(12)
Women (n (%))	13 (16%)	59 (26%)	23 (19%)
Asian ethnicity (n (%))		134(59%)	
Risk factors			
Hypertension (n (%))	56 (70%)	102 (45%)	80 (66%)
Current smoker (n (%))	49 (61%)	50 (22%)	57 (47%)
Diabetes (n (%))	14 (18%)	69 (30%)	26 (21%)
Other factors			
Asthma	0	n/a	4(3%)
Beta blocker use	63(79%)	19(8%)	69 (57%)

2.4 Summary

In this chapter the study groups have been described for the various chapters. The demographics and risk factors for each cohort is summarised in Table 10.

Cohort 1, the group examined in Chapters 4 and 5, differ from many previous studies of CTCA as all had known coronary artery disease. Cohort 2, examined in Chapter 6, is recruited from an area with high levels of poverty and deprivation and has a high proportion of South Asian patients. Cohort 3, examined in chapter 3, has a low representation of asthmatics and a high proportion of people with known ischaemic heart disease.

3. HEART RATE AND RHYTHM DURING CT CORONARY ANGIOGRAPHY

3.1 Abstract

Background

The clinical application of cardiac computed tomography (CT) is increasing but heart rate control is often required to prevent motion artefact.

Methods

In the present study I describe a protocol for heart rate control in patients undergoing outpatient CT coronary angiography. Among 121 consecutive patients, 75 (61.9%) with a resting heart rate >60 bpm required rate control medication. My protocol called for oral metoprolol 100mg to be given 60 minutes before scanning, patients in whom beta-blockers were contraindicated receiving oral verapamil 240mg. Additional 5mg intravenous boluses (maximum for both drugs 15mg) were given if the heart rate remained >60 bpm prior to scanning.

Results

Of 71 patients treated with oral metoprolol 59 (83%) achieved a rate ≤65bpm and 46 (65%) achieved a heart rate of ≤60bpm during the CTCA scan. The 4 patients receiving verapamil all had a poor rate response with heart rates >70bpm at time of scanning. There were no adverse events due to rate control medication. Image quality was closely related to heart rate, severe motion artefact (Grade 3) occurring in only 0.9% of patients with a rate ≤60bpm compared with 50% of patients with a rate >70bpm.

Conclusion

The administration of oral metoprolol according to the protocol described in my study is a safe and effective way of reducing heart rate and improving scan quality in the majority of patients undergoing CT coronary angiography.

3.2 Introduction

CT coronary angiography (CTCA) is a technique that has recently developed sufficiently to begin to be used for the visualisation of the coronary arteries avoiding the invasive technique of coronary angiography. Imaging the coronary arteries poses many difficulties for CT technology as the coronary arteries are small, often calcified and move both with respiration and the cardiac cycle. In most patients it is possible to eliminate motion due to breathing by performing the scan during a breath hold.

It is the movement of the heart that is most influenced by the heart rate and rhythm. Any imaging modality assessing the heart must have a fast temporal resolution in order to prevent blurring of the image, the temporal resolution being the time required to obtain a single image. Conventional invasive coronary angiography has a temporal resolution between 5 and 20milliseconds (ms) and is capable of reliably imaging the coronary arteries without any blurring from cardiac motion. CT technology has gradually evolved from a temporal resolution of several minutes in early scanners to requiring less than 100ms to obtain an image with current dual source systems. From the early days of CT technology, Alfidi[221] postulated that a temporal resolution of less than 50ms was required to obtain detailed cardiac imaging. By measuring the velocity with which structures move, Ritchie[222] calculated that scan time (temporal resolution) of less than 20ms was required to avoid artefacts. As has been shown earlier, CT technology uses data from the attenuation of x-rays passing through an object from different angles. In a still object the scanner may acquire these images without concern for temporal resolution, but in a moving object the scanner must acquire sufficient data to image the object in a short period of time to avoid artefacts from the object being in different places when data are acquired from different angles. In single source scanners such as 64 slice CT scanners there is one x-ray source and one x-ray detector that rotate in unison around the object being scanned, in this case a patient. The speed with which sufficient data can be acquired to reconstruct an image of the patients heart is thus directly related to the speed with which the x-ray source and detector rotate. The gantry rotation time is the time it takes the scanner to complete one rotation around the patient.

In the absence of divergence of the x-ray beam a 360 degree scan would duplicate data acquisition of a still object when the source and detector are in opposite configurations. In Figure 14 when the scanner is in position (a) the x-ray source is anterior to the patient and x-rays pass from anterior to posterior and are detected by the detector lying posterior to the patient. If the gantry rotates 180 degrees to position (b), the x-ray source and detector are in opposite configurations and the x-rays pass through the same part of the patient from posterior to anterior. Essentially identical data are acquired, ie the same attenuation of the x-ray occurs as it passes along this path through the patient, irrespective of whether the x-rays pass from anterior to posterior or posterior to anterior.

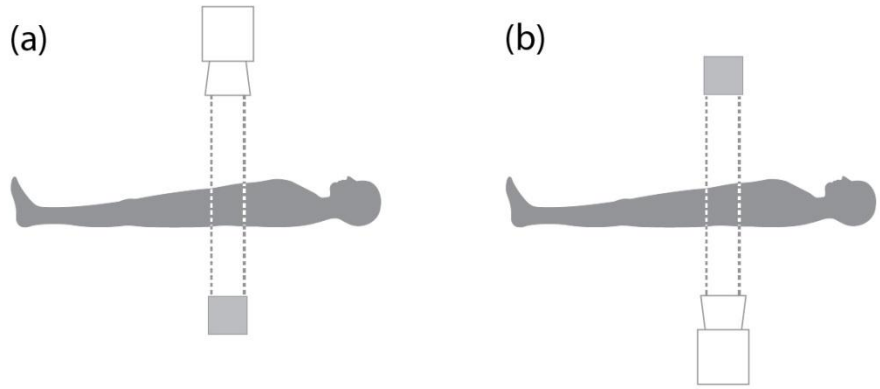


Figure 14 Tube and detector in opposite configurations

Thus a full data set can be acquired from 180 degrees of rotation and the scanner temporal resolution is approximately half the gantry rotation speed. A small allowance needs to be made for the fan angle of the x-ray beam.

Multi-segment reconstructions use data from more than one cardiac cycle to generate an image at a single level.[93] Using these techniques, the relationship between temporal resolution and heart rate loses its simple linear behaviour and [223] becomes a function of the number of segments used and the rotation speed of the scanner. As can be seen in Figure 15 taken from Greuter[223] at lower heart rates multisegment reconstructions often provide little advantage over single segment reconstructions,

but as the heart rate increases the mathematical advantage becomes greater for multisegment reconstructions. The point at which multisegment reconstructions become more beneficial is related to the rotation time of the scanner, with faster scanners favouring single segment reconstructions until higher heart rates than scanners with slower rotation times.

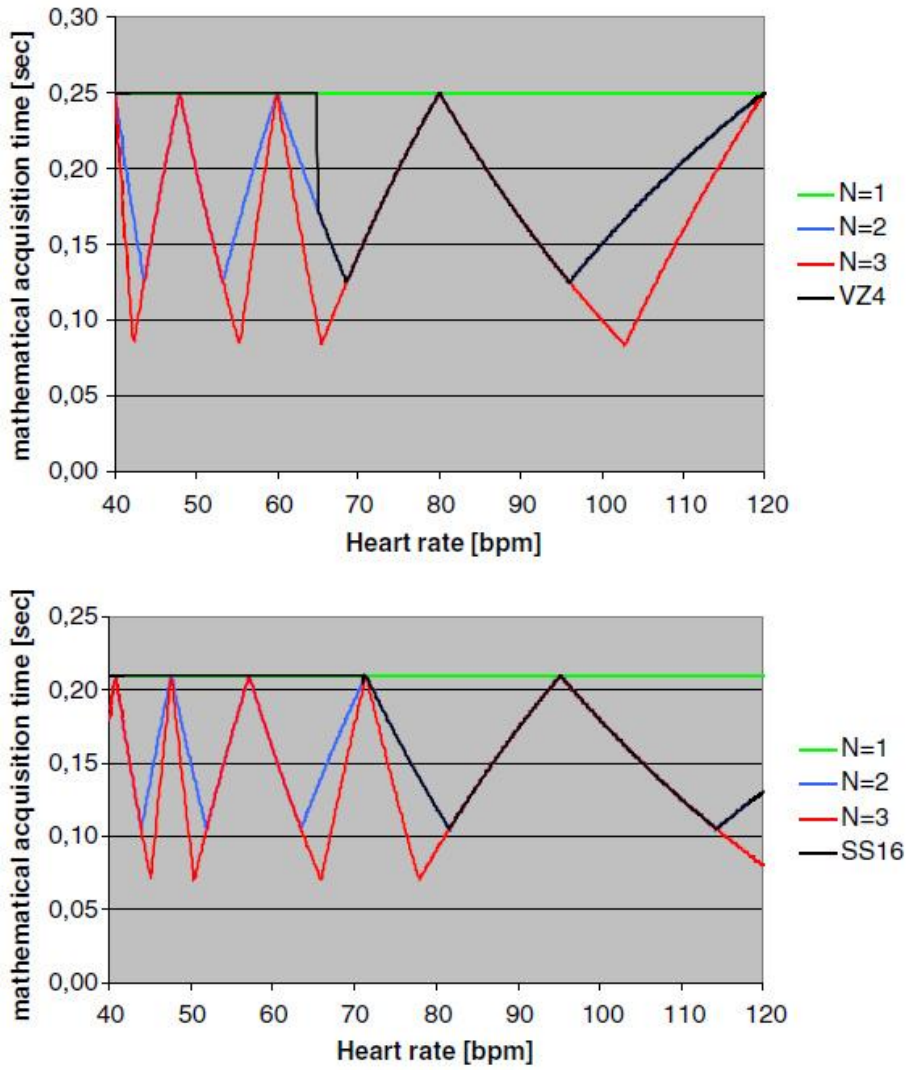


Figure 15 Calculated temporal resolution as a function of heart rate of a reconstruction algorithm using N segments. The top graph represents a scanner with rotation time of 500ms and the bottom graph 420ms. In addition, the temporal resolution of the Siemens Volume Zoom (VZ4) and the Siemens Somatom Sensation 16 (SS16) are shown.[223]

Halliburton[224] examined the image quality comparing these techniques in 78 patients using a 4 slice scanner with a 500ms rotation time and a second group of 28 patients using a 12 slice scanner with a 420ms rotation time. It was shown that the theoretical mathematical advantage of multisegment reconstruction did not translate into a measurable difference in image quality. As the mechanical temporal resolution of scanners improves, the theoretical advantage of multisegment reconstructions will be further reduced and is likely to become less applied in clinical settings.

In an attempt to image the heart when it is moving the least, CTCA scanners often try to use data from the period of the cardiac cycle when the heart is least mobile. This period of time is during filling of the ventricle in mid diastole and is called diastasis.[225] There is also a shorter period of time at peak systole when the heart is fully contracted and momentarily stationary before it relaxes at the beginning of diastole. It can be seen that the scan or the reconstruction of data from the scan must be linked to the cardiac cycle in order to generate images from these periods to reduce motion artefacts. The simplest means to do this is to co-ordinate with the ECG which acts as a consistent indicator of the cardiac cycle. Once the beginning and end of the cardiac cycle can be identified from the r wave on the ECG trace it is possible to select a time point relative to this that coincides with diastasis. There are two main methods of documenting this either as a percentage of the cardiac cycle (measured from the preceding r-wave) or as an absolute value in ms. Absolute values can be taken from either the preceding r-wave and the convention is that this is recorded as a positive number (eg 600ms) or from the following r wave in which case a negative number of ms is used (e.g. -300ms) as illustrated earlier in figure 9. Diastasis cannot be defined exactly by timing within the cardiac cycle as it is dependent on multiple other factors such as contractility and relaxation properties of the myocardium and the filling state of the patient.[226] Diastasis does however occur at similar times within the cardiac cycle. Hong,[227] using a 4 slice scanner found that this was usually at 50% of the r-r interval for the RCA and later at 50-60% for left anterior descending artery (LAD) and 60% for left circumflex arteries (LCx). It is not possible to transfer these directly to other scanners given the difference in technology and reconstruction algorithms,

however the finding that the RCA is better imaged at an earlier time in the cardiac cycle should still apply. In my institution it has been observed that the optimum cardiac phases are consistently later than those published by Hong and this may be due to differences in the way the reconstructions are extracted relative to the starting point.

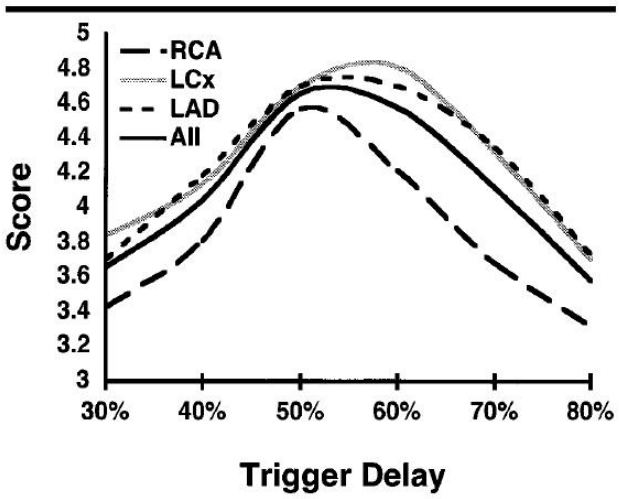


Figure 16 Image quality versus delay of ECG-gated reconstruction for individual and all coronary arteries.[227]

An alternative method for identifying the phase in the cardiac cycle where there is least motion is the use of a kymogram as described by Kachelriess.[228] This technique uses the raw data from an MDCT acquisition to calculate the centre of mass (COM) at a given level within a scan range. Changes in this COM are tracked and the point of minimum and maximum variation in the COM can be identified and used as a marker for planning reconstructions in the same way as a the r waves on ECG. Kachelriess compared the technique to ECG gated reconstructions from the same scans and showed close correlation.

64 slice scanners have detectors between 3 and 4 cm in width and thus cannot cover the full volume of the heart within one rotation. In order to image the whole of the coronary arterial tree, data from multiple rotations of the scanner must be combined. In order to complete multiple rotations within the diastasis of one cardiac cycle would

require vastly faster rotation times than is currently available and at such speeds, image noise levels are likely to be substantially increased. A CT scanner gantry has a significant mass, and to be able to rotate the entire mechanism at this speed would encounter significant challenges due to the huge forces involved. It is unlikely that such changes will occur in the near future if at all. Thus with the limited coverage of 64 slice scanners the image of the coronary artery tree must be compiled from rotations taken in more than one cardiac cycle. With larger area detectors such as those on 320 slice scanners it is possible to image the heart in one or two rotations and thus this problem is overcome.

Wang's work exploring coronary artery motion by means of assessing invasive coronary angiograms with temporal resolution of 33ms[229] shows that the right coronary artery (RCA) has the shortest rest period (66-200ms mean 120ms) and the largest velocities when mobile and moves the largest distance (Figure 17). As heart rate increases it is diastasis that shortens most as the time required to complete the cardiac cycle must decrease and the amount of time required for ventricular contraction in systole is less variable.[230]

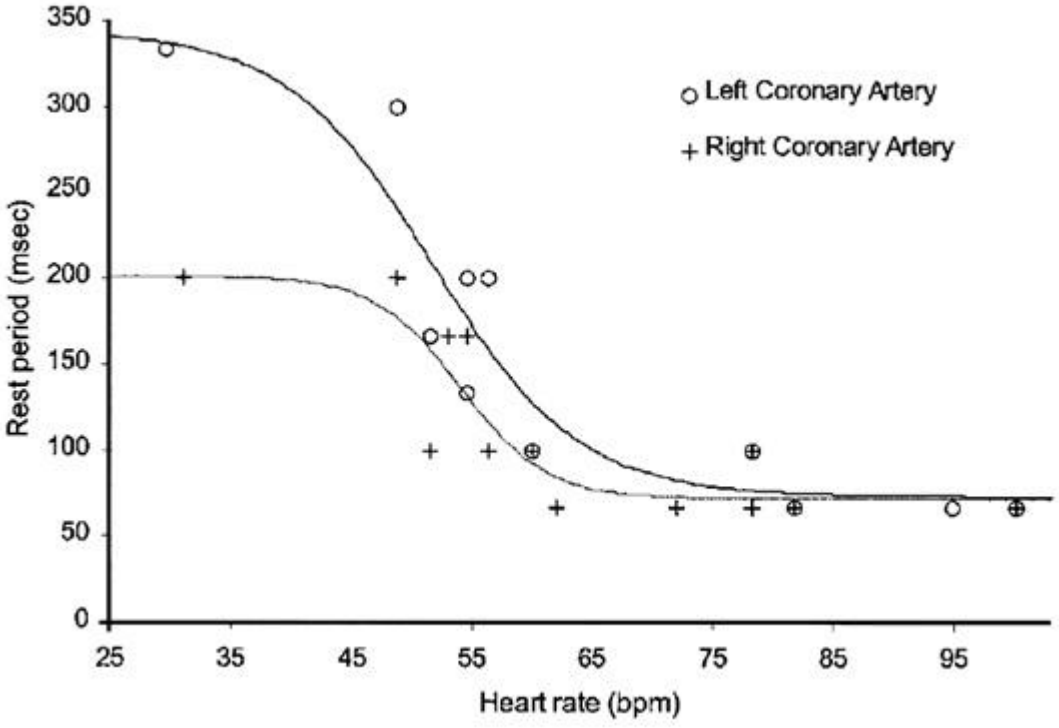


Figure 17 Rest period for left and right coronary arteries at different heart rates[229]

Nieman[231] investigated the relationship between heart rate and the number of assessable coronary segments on a 4 slice scanner with rotation time of 500ms. It was shown that more segments were evaluable at lower heart rates. The cohort of 78 patients was split into three groups depending on heart rate and the sensitivity, specificity and positive and negative predictive values were calculated for each group. As can be seen in the table below, although the small numbers result in wide confidence intervals, the group with low heart rates (mean 55.8bpm, SD 4.1) had improved diagnostic accuracy compared to those in the faster group (mean 81.7bpm, SD 8.8).

Table 11 Diagnostic accuracy of a 4 slice CT scanner for detecting ≥50% coronary artery stenoses at varying heart rates[231]

		Groups			
		All (n=78)	Group 1 (n=26)	Group 2 (n=26)	Group 3 (n=26)
Baseline characteristics					
Heart rate (beats/min)	Mean (SD)	68.0 (12.1)	55.8 (4.1)	66.6 (2.8)	81.7 (8.8)
	Range	49 to 103	49 to 62	63 to 72	73 to 104
Age (mean (SD))		56.9 (10.1)	58.3 (9.7)	58.9 (9.7)	53.4 (10.2)
Sex (male/female)		57/21	18/8	23/3	16/10
⩾50% stenotic lesions*		57 (76)	29 (34)	19 (23)	9 (19)
Stents		31	9	15	7
Assessability					
Relevant segments†		741	244	251	246
Assessable segments‡		505 (68%)	191 (78%)	182 (73%)	132 (54%)
Causes of non-assessability‡	Cardiac motion	73 (10%)	10 (4%)	15 (6%)	48 (20%)
	Calcifications	40 (5%)	17 (7%)	15 (6%)	8 (3%)
	Other causes¶	35 (5%)	5 (2%)	4 (2%)	26 (11%)
	Non-specific	88 (12%)	21 (9%)	35 (14%)	32 (13%)
Diagnostic accuracy (95% CI)					
Assessable coronary segments	Sensitivity	84% (74% to 92%)	97% (84% to 100%)	74% (52% to 89%)	67% (33% to 90%)
	Specificity	95% (93% to 96%)	96% (94% to 97%)	94% (91% to 96%)	94% (91% to 95%)
	Positive predictive value	67% (58% to 73%)	82% (71% to 85%)	58% (41% to 70%)	43% (21% to 58%)
	Negative predictive value	98% (97% to 99%)	99% (97% to 100%)	97% (94% to 99%)	97% (95% to 99%)
Sensitivity including non-assessable segments (95% CI)§		63% (54% to 71%)	82% (69% to 91%)	61% (42% to 77%)	32% (15% to 50%)
Accuracy at patient level**		56%	73%	54%	42%
Causes of misinterpretation	Total misinterpretations	33	7	15	11
	Calcification	17	5	8	4
	Cardiac motion	11	–	5	6
	Other causes	5	2	2	1

*The number of lesions including non-assessable segments given in brackets.
†All ⩾2.0 mm segments, but excluding segments containing stents.
‡Percentages of the (relevant) ⩾2.0 mm segments given in brackets.
¶Other causes include: respiratory motion, blending with adjacent contrast filled structures (vein, right ventricle), artefacts from pacemaker wire.
§Sensitivity including undetected lesions in non-assessable segments as false-negative.
**Percentage of patients with completely true positive or true negative diagnoses, including undetected lesions in non-assessable segments as false negative.
CI, confidence interval.

Working with the same scanner, Hong rated scans with a five point scale for quality and artefact and found that patients with lower heart rates had higher image quality scores.[227]

Contemporary 64 slice scanners have faster rotation times of around 330-370ms and increased coverage compared to the 4 slice scanners used in the studies above.

Leschka assessed the impact of heart rate on image quality using a 64 slice scanner with a gantry rotation time of 370ms.[232] The study had a low mean heart rate during scanning of 63.3 beats per minute(bpm) ±13.1bpm and very few scans that were rated as having severe artefacts and no coronary artery was rated as uninterpretable. No correlation was found between mean heart rate and image quality in LAD and RCA images, and only a weak correlation in the LCx images. There was however a strong correlation between the variability of heart rate during scanning and image quality.

Groen[233] used a moving heart phantom to evaluate the effect of different heart rates on image quality using a 64 slice scanner with a rotation time of 330ms. In this study stents were placed in the cardiac phantom and filled with air. The average Hounsfield unit (HU) was measured on the images obtained from the air filled lumen of the stents, the supposition being that the more artefact the greater the HU value would appear to be within the stent, the true HU value of which should be very low in keeping with the air that fills the lumen. The scan images were also visually graded for quality by two readers. It was shown that there was an increasing HU value with increasing heart rate. Quality scores also fell as heart rate increased, supporting the concept that low heart rates are key to reducing artefact in 64 slice CTCA.

Heart rate is not the only parameter of the timing of cardiac motion that is of particular importance to CTCA. Heart rhythm and the variability of the heart rate is of extreme importance. In the era of 64 slice CT scanners nearly all research studies exclude patients with arrhythmias such as atrial fibrillation, although with the faster dual source scanners the susceptibility to arrhythmia is reduced and successful scanning in the presence of arrhythmia have been reported. Atrial fibrillation results in a near random heart rhythm with variations in the cardiac cycle length and variations in the timing of periods of reduced cardiac motion. As has been shown earlier, cardiac CT scanners can use ECGs to time the actual acquisition of a scan or modulation of x-ray power. Reconstruction algorithms use data from certain time points in the cardiac cycle in order to reduce artefact and if multisegment reconstructions are used data

from more than one cardiac cycle has to be used to construct an image at a given level. When the cardiac cycle length is erratic it becomes increasingly difficult to time when the heart is in the same phase of the cardiac cycle. Atrial fibrillation usually results in the greatest beat to beat variability in heart rate, but even in patients in sinus rhythm, extrasystoles or sinus arrhythmia can be sufficient to reduce image quality.[232]

CTCA is generally performed during a breath hold to reduce artefact originating from change in the position of the heart due to movement of the diaphragm and ribcage with breathing. Unfortunately the process of breath holding itself can introduce variations in the heart rate due to normal physiological processes.[227, 231]

The importance of a low heart rate during CTCA acquisition has been demonstrated above. Most centres performing CTCA have developed their own protocols for the administration of medications to reduce the heart rate at the time of the scan. Given that intravenous contrast administration is required to perform a scan, an intravenous cannula has to be inserted and therefore regimes with both oral and intravenous medications have been used.

3.3 Regimes in use

A systematic review of the literature for studies examining CTCA was performed. Publications were identified by searching medline via pubmed and reviewing citations of all identified studies and citations of reviews on the subject. Any study that involved performing CTCA on human subjects in a non acute setting was included. Studies that did not state their heart rate strategy were excluded. For included studies details of the rate control regime used and the mean heart rate at time of scan where available where recorded. The data are summarised in Table 12 below. It can be seen that there are many different approaches to rate control in the context of CTCA. All strategies employed administration of beta blockers and by far the commonest is oral metoprolol at a dose of 50-100mg. Other studies used oral atenolol and one study employed esmolol. Most studies had a fixed dose strategy, but few had a variable dose strategy with higher doses given to subjects with higher heart rates. Only one study administered medications before the day of the scan and most administered

medications between 45 mins and an hour prior to the scan being performed. The protocol to follow when the subjects heart rate exceeded target after the initial medication was less well defined, but where stated, included administration of further intravenous doses of metoprolol up to 30mg.

Table 12 Rate reduction regimes in published studies

Author	Slices	Rotation (ms)	Arrhythmias Excluded	Pre-Rx Target (bpm)	Drug	Route	Dose (mg)	Time pre-CT (mins)	Post-Rx Target (bpm)	Action if HR>Target	Scan HR (mean±SD bpm)
Nieman	16		Yes	65	metoprolol	oral	100	60	none	none	56±6
Ropers	16		Yes	60	atenolol	oral	50	60			
Martuscelli	16		Yes	All	atenolol	oral	50-100	OD 3/7	70	exclude	59±5
Kuettner	16		Yes	50	metoprolol	oral	50-100	45			64±10
Mollet	16	420	Yes	65	metoprolol	oral	100	60			58±8
Kuettner	16	375	Yes	65	metoprolol	oral	50-100	45			64±9
Mollet	16	375	Yes	70	metoprolol	oral	100	60			57±1
Achenbach	16	370	Yes	60	atenolol	oral	100	60	60	≤20mg iv metoprolol	58±6
Hoffman	16	420	Yes	75	metoprolol	iv	≤20	0			69±12
Garcia	16	n/a	Yes	65	metoprolol	iv	≤15	0			59±9
Leber	64	330	Yes	70	metoprolol	oral	50	60			62±13
Raff	64	330	Yes	65	atenolol	oral	100	60			
				50-65	atenolol	oral	50	60	65	≤30mg iv metoprolol	65±10
Mollet	64	330	Yes	70	metoprolol	oral	100	45			
				80	lorazepam	oral	1				58±7

Author	Slices	Rotation (ms)	Arrhythmias Excluded	Pre-Rx Target (bpm)	Drug	Route	Dose (mg)	Time pre-CT (mins)	Post-Rx Target (bpm)	Action if HR>Target	Scan HR (mean±SD bpm)
Pugliese	64	330	Yes	70	metoprolol	oral	100	60			58±6
Malagutti	64	330	Yes	65	metoprolol	oral	≤100	45		proceed	60±7
					lorazepam	oral	1	45			
Fine	64	330	n/a		metoprolol	oral / iv	n/a				n/a
Ropers	64	330	Yes	60	atenolol	oral	100	60	60	≤20mg iv metoprolol	60±9
Schuijf	64	400	Yes		n/a					1 excluded	60±11
Schlosser	16	420	Yes	70	esmolol	iv	n/a	n/a		exclude	64±5
Burgstahler	16	375	n/a	n/a	metoprolol	oral	50-100	30			68±11
Anders	16	420	Yes	60	atenolol	oral	50	60			63
Stauder	16/64		Yes	50	metoprolol	oral	50-100	45			67±9
Pache	64	330	n/a	65	metoprolol	oral	50-100	n/a		proceed	63±7
Ropers	64	330	Yes	60	atenolol	oral	100	60	60	≤20mg iv metoprolol	59±9

3.4 Rate reducing drugs; pharmacodynamics and pharmacokinetics

The choice of drug to use to reduce the heart rate in patients undergoing CTCA must consider the following issues: Efficacy in reducing heart rate, safety, route of administration, speed of onset, half life and duration of action, availability and familiarity, local facilities and logistics. When considering such medications the range of rate reducing medications that are potentially available to the physician is large. As most cardiac CT with 64 slice scanners is restricted to patients in sinus rhythm the ideal agent would be active on the sinus node to reduce heart rate whilst preserving sinus rhythm. Drugs working on other parts of the conduction system are not likely to be beneficial in this setting, as the introduction of heart block is potentially dangerous and may lead to irregularity of rhythm.

Potential drugs that work in this manner are beta blockers, calcium channel blockers and recently ivabradine.

Beta Blockers are a group of drugs that are antagonists for β-adrenoreceptors found in many tissues in the body. There are two main types of β-adrenoreceptors, β1 and β2 with β1 found predominantly in the heart where they are responsible for the positive chronotropic and inotropic effects of catecholamines. Beta blockers, being antagonists to these receptors have a negative chronotropic and inotropic effect on the heart by blocking the sympathetic 'tone' that is generally present at a resting state. Different drugs have differing selectivity for β1 and β2 adrenoreceptors, and thus have varying degrees of non-cardiac activity. The most important side effect of beta blockers is due to their action on β2-adrenoreceptors in the lungs that can cause bronchoconstriction and is particularly important in asthmatic patients.[234] The table below outlines some of the important features of beta blockers used in UK practice compiled from UK MHRA SPCs and FDA monographs and other reviews on this topic.[235] It should be noted that metoprolol succinate is not available in UK and has different pharmacodynamic properties to metoprolol tartrate.

It can be seen that metoprolol and atenolol have the nearest qualities to our ideal agent for an orally administered drug. Being relatively selective to β1 adrenoceptors reduces likelihood of side effects such as bronchoconstriction. They have fast onsets compared with other beta blockers and relatively short half-lives, potentially improving safety. Metoprolol has slight advantage over atenolol with faster onset of action and its shorter duration increases safety. This is reflected in its extensive utilisation in centres undertaking CTCA. Esmolol is of interest given rapidity of action and short duration making it safe but lack of familiarity and the need for a continuous infusion may deter some centres from using it. It should be noted that although the speed of onset of action is fast for intravenous esmolol, metoprolol and atenolol, titration over a period of time rapidly increases the time to reach target heart rate, as it is necessary to wait till the maximum efficacy of any bolus is reached before administering a further bolus, and during this time patients must be carefully monitored.

Calcium channel blockers are another possible group of medications that could be applied in this context. Calcium channel blockers disrupt movement of calcium through L-type calcium channels in the cell membrane. Blockade of voltage gated calcium channels in cardiac myocytes and smooth muscle in blood vessels, leads to decreased intracellular calcium levels. Intracellular calcium is required for contraction and thus calcium channel blockers reduce contractility of cardiac muscle and cause vasodilation of blood vessels, together this results in a fall in blood pressure. In cardiac sinotrial nodal and atrioventricular nodal tissue, L-type calcium channels play an important role in pacemaker currents that regulate heart rate. Blocking L-type calcium channels reduces the speed with which calcium can enter the nodal cells and thus slowing the time taken for the cell to depolarise and reach an action potential threshold. This prolonged time to depolarisation relates to a decreased sinus node rate, and also reduces conduction through the atrioventricular node. There are three classes of calcium channel blocking agents; dihydropyridines have a predominant effect on smooth muscle and less effect on cardiac calcium channels, whereas non-dihydropyridines of the phenylalkylamine (verapamil) and benzothiazepine (diltiazem)

classes have more cardiac effect and vascular effects. Of the two non-dihydropyridines, verapamil has the greater cardiac effect, whilst diltiazem has both cardiac depressant and vasodilator actions. Verapamil, therefore is more likely to be useful in the setting of CTCA, reducing the likelihood of unwanted hypotension whilst maximising rate limiting potential.[236-238]

Verapamil can be administered in oral or intravenous forms. After oral administration, peak plasma concentrations are attained within 1-2 hours and the half life is 5-12 hours with conventional release preparations.[239] After intravenous injection maximum effect on heart rate is at 10-15 minutes and effects last 1-6 hours.

Ivabradine is a new and interesting drug that acts on the I_f channel in the sinoatrial node to reduce heart rate in sinus rhythm. It has no effect on blood pressure or cardiac output and is thus a potentially ideal candidate for use in the setting of CTCA.[240] Majewski[241] demonstrated significant reduction in heart rate with an oral 5 day regime of ivabradine when compared with placebo. Pichler[242] compared a single dose of ivabradine 15mg with metoprolol 50mg and found similar reductions in heart rate but less reduction in blood pressure in the ivabradine group. There has also been development and assessment of an intravenous form of ivabradine by the manufacturer but efficacy data are not available.

Table 13 Characteristics of rate reducing agents

Generic Name	Route of administration	Dose	Selectivity	Onset	Duration of action
Propranolol	Oral / IV	1-10mg IV 40mg-160mg PO	β1 / β2	5mins IV 2hrs PO	2-3hrs IV 3hrs PO
Atenolol	Oral / IV	2.5-20mg IV 25-100mg PO	β1	5min IV 1-4hrs PO	12hrs IV 24hrs PO
Metoprolol tartrate	Oral / IV	5-15mg IV 50-100mg PO	β1	10mins IV 1hr PO	5-8hrs
Bisoprolol	Oral	1.25-10mg PO	β1	1-4hrs	24hrs
Carvedilol	Oral	3.125-25mg PO	β1 / β2	1.5-7hrs	12hrs
Esmolol	IV	500mcg/kg/min for 1 min loading 50-200mcg/kg/min infusion	β1	1min	5-10mins

Whilst it is clear that there is widespread use of a number of medications for rate reduction prior to performing CTCA there is very limited evidence of efficacy in this specific setting. In the only study of this, Shim[243] assessed the efficacy of a regime using oral propranolol at a dose of 20mg one hour prior to scanning which could be repeated if subjects' heart rates had not fallen below the target heart rate of 65bpm. It was shown that there was a significant difference in mean heart rate in subjects not receiving the propranolol regime (mean HR 80.3 S.D. ±18.6 bpm) and those who did receive propranolol (mean HR 54.0 S.D±6.7 bpm). The two groups studied compared were likely to have significant confounding differences as one group were volunteers and the other had known ischaemic heart disease and thus likely to be on rate reducing medication as part of their regime. Propranolol would also not seem to be the most logical choice for use in this setting given its relatively slow onset and lack of selectivity.

In my study the standardised regime for heart rate lowering that had previously been developed by myself and routinely employed in our institution was examined in a cohort of 121 outpatients attending our radiology department. Given the data discussed above, and particularly the data in Table 13 the regime used oral metoprolol as the preferred agent supplemented with intravenous metoprolol and oral and intravenous verapamil in those patients with specific contraindications to beta blockers.

3.5 Methods

Ethics. Heart rate reduction using beta-blockers or verapamil is a clinical requirement for patients undergoing diagnostic CT coronary angiography (CTCA). I was advised that ethical approval was not, therefore, needed for this study.

All patients undergoing CT coronary angiography (CTCA) were managed using the rate control regime documented below. Blood pressure and heart rate were measured before the scan and use of rate slowing medication (beta-blockers, verapamil) was

documented. The mean heart rate during the part of the scan used to reconstruct images of the coronary arteries was recorded. All patients in this study were scanned irrespective of heart rate, but in clinical situations consideration should be given for cancelling the scan and considering alternative means of assessment or postponement until further techniques (discussed later) to ensure adequate heart rate control can be utilised.

3.5.a Patient demographics

Patients included those undergoing CTCA for clinical indications (n=24) and as part of research studies (n=97). Due to the inclusion and exclusion criteria for the research studies, my cohort includes a larger proportion of patients with known coronary artery disease and a smaller proportion with asthma than would be expected in the general outpatient radiology service.

3.5.b Rate lowering regime

Patients were asked to attend the radiology department one hour prior to the scheduled scan time. All patients were in sinus rhythm. The blood pressure and heart rate were checked using an automatic sphygmomanometer. A short medical questionnaire was completed to cover the standard contrast safety screening and the contraindications to rate control medications.

The target heart rate was defined as 60bpm and patients above this threshold were treated with either a beta-blocker (metoprolol) or a calcium channel blocker (verapamil) if the systolic blood pressure was ≥110mmHg. Metoprolol was used preferentially with verapamil in patients with contraindications to beta blockers.

Contraindications specific to beta blockers were asthma that required the use of regular inhaled bronchodilators. Contraindications that applied also to verapamil were drug allergy, any degree of atrioventricular heart block or severe aortic stenosis.

Patients requiring heart rate control were treated according to the protocol summarised in Figure 18. They were given 100mg oral metoprolol (n=75) except those in whom beta blockers were contraindicated who received 240mg of oral verapamil

(n=4). After one hour patients were prepared for CTCA and connected to the integrated electrocardiogram monitor on the CT scanner. If the target heart rate of ≤60bpm had not been achieved additional metoprolol or verapamil was administered as 5mg slow intravenous boluses (maximum for both drugs 15mg) at 5 minute intervals under continuous electrocardiographic monitoring. Patients received 1mg glyceryl trinitrate sublingually and thereafter all patients were scanned irrespective of heart rate. Patients were allowed to leave the department one hour after the last oral dose or 30 minutes after last intravenous dose of rate control medication.

3.5.c Scan parameters and final heart rate

Scans were performed using a Siemens Somatom Sensation 64 multi slice CT scanner with rotation time of 330ms and 64x0.6mm collimation. All patients initially underwent a topogram and a low dose sequential calcium scoring sequence. A test bolus scan was performed to ascertain circulation time for triggering of the main CTCA scan. The test bolus scan involved the injection of 20ml of contrast (Iomeron 400) at 5ml/sec followed by 20ml of Normal Saline at 5ml/sec. The final CTCA scan required the injection of 80ml of contrast (Iomeron 400) at 5ml/sec and 40ml of Normal Saline at 5ml/sec.

The final rate was documented automatically by the CT scanner which calculates the mean heart rate during the approximately 12 second acquisition of the CTCA scan. Electrocardiograms were visually checked to exclude miscalculation of heart rate due to extrasystoles or artefact.

3.5.d Quality scoring

All scans were reviewed and graded for motion artefact with the scoring system in Table 14 below.

Table 14 Quality scoring levels

Grade	Criterion
1	No significant motion artefact
2	Minor motion artefact affecting evaluation in 1 segment
3	Severe motion artefact affecting 2 or more segments

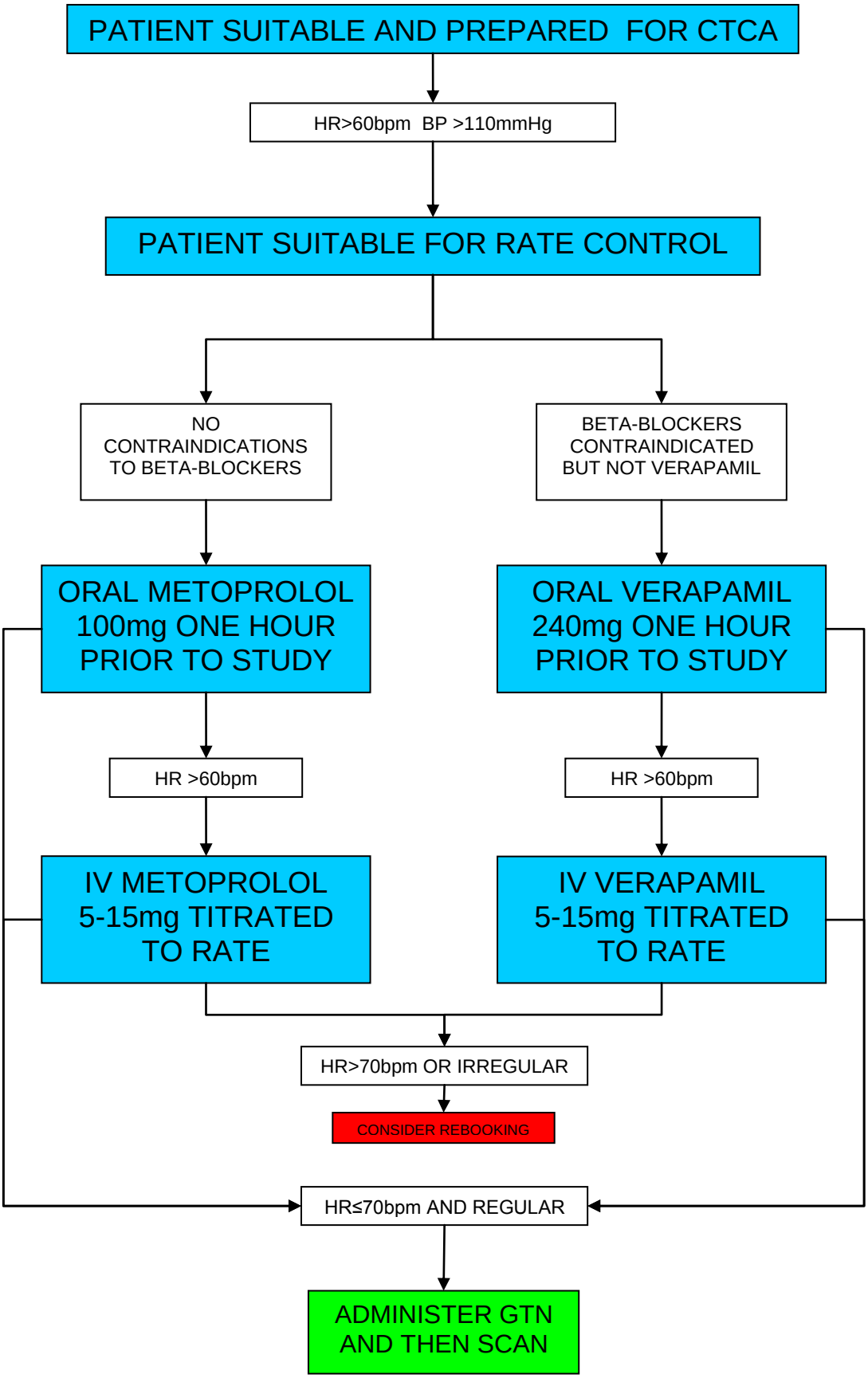


Figure 18 Suggested rate reducing regime for clinical use

3.6 Results

Heart rate data were recorded from 121 patients undergoing CTCA, 46 of whom required no further rate control medication. Of the 75 patients (62%) who required rate control medication 71 received metoprolol and 4 received verapamil due to co-existent asthma. Figure 2 shows the flow of patients through the rate control protocol.

Patients with a resting heart rate >60bpm and requiring rate control were less likely to have known CAD and be taking beta blockers than patients not requiring rate control (chi square $p<0.001$), but there were no other differences between the groups (Table 15). Of the 77 patients previously on a calcium channel blocker or beta blocker, 34 (44%) required additional rate control medication.

Table 15 Patient characteristics by requirement for rate control therapy

	Patients requiring rate control n=75	**Patients not requiring rate control** n=46
Beta blocker	29 (39%)	40 (87%)
Calcium channel blocker	12 (16%)	8 (17%)
Ca-channel and beta blocker	7 (9%)	5 (11%)
Diabetic	17 (23%)	9 (20%)
Smoking history (current or >20 pack years previously)	34 (45%)	23 (50%)
Hypertension	48 (64%)	32 (70%)
Hyperlipidaemia	64 (85%)	38 (83%)
Known coronary artery disease	44 (59%)	38 (83%)
Blood pressure (mmHg)	138/83 (±17.6/±10.2)	133/77 (±22.2/±12.3)
Initial heart rate (bpm)	75 (±9.7)	56 (±4.5)

Of the 71 patients receiving rate control with oral metoprolol 59 (83%) achieved a rate ≤65bpm and 46 (65%) achieved a heart rate of ≤60bpm during the CTCA scan. The mean heart rate in this group was 59±7.7bpm with a rate reduction of 17±9.7bpm. In the 12 patients requiring additional IV metoprolol only 3 had a heart rate ≤65bpm at

time of scanning. The 4 patients receiving verapamil had poor responses to rate control medication with heart rates >70bpm at time of scanning.

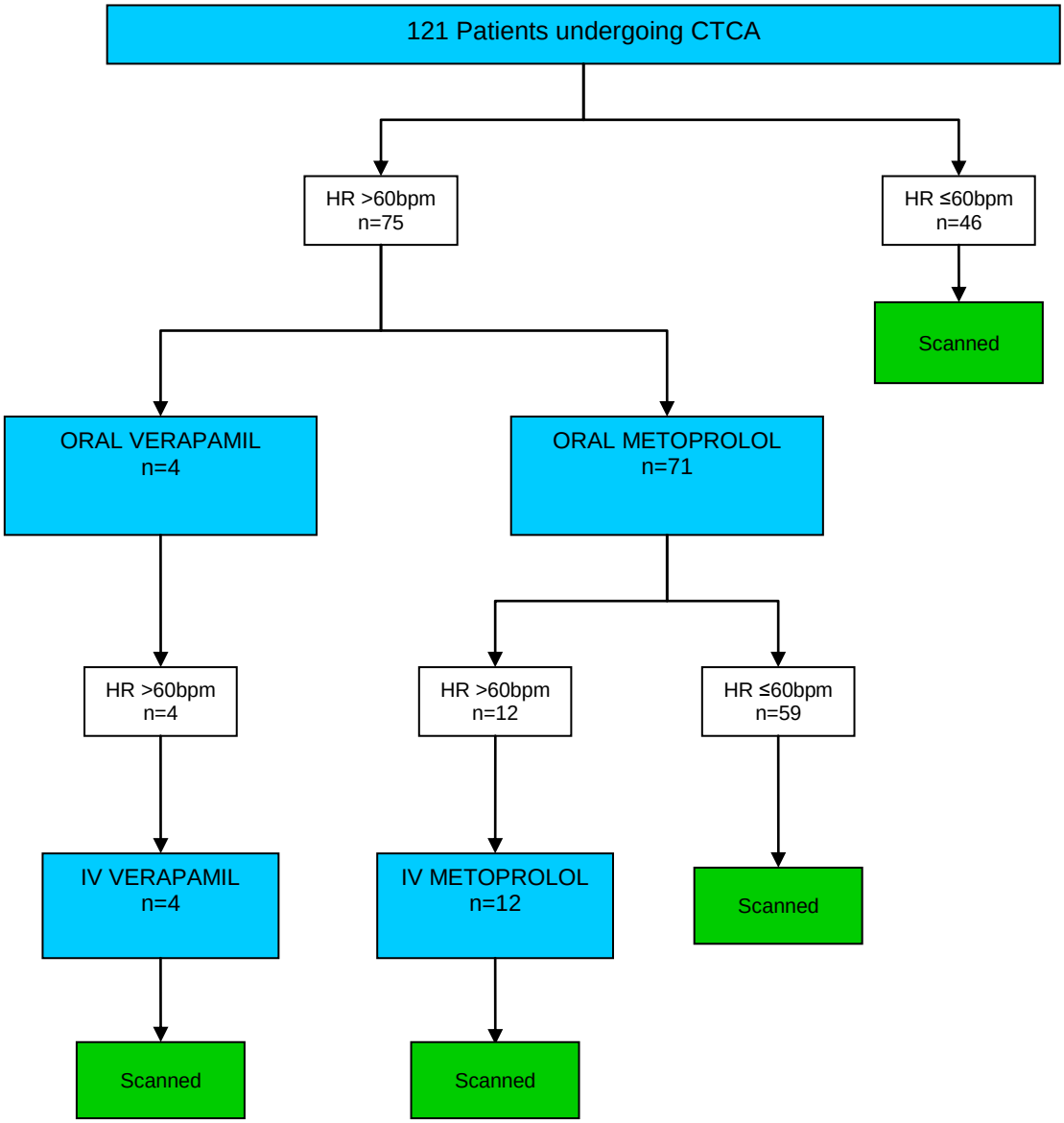
There were no adverse effects in any patients related to beta blocker or calcium channel administration with no reports of pre-syncope in any patients. Two patients experienced minor contrast extravasation which settled with cold compression. One patient found to have severe aortic stenosis on the scan was already taking a beta blocker and had not required additional rate limiting medication.

Table 16 shows the relation between heart rate during CTCA scanning and motion artefact. Among the 77 patients with a heart rate ≤60bpm, 76 (99%) had little or no motion artefact (Grade 1 or 2) but in the 16 patients with a heart rate >70bpm severe motion artefact (Grade 3) was present in 50% of patients. The proportion of patients with severe motion artefact (Grade 3) increased with heart rate.

Table 16 Heart rate at scan time compared with quality score

Rate at scan time (bpm)	**Grade 3**	**Grade 2**	**Grade 1**
≤60 (n=77)	1	7	69
61-70 (n=28)	5	6	17
>70 (n=16)	8	6	2

There is a clear relationship between heart rate and quality score with worse quality scores in patients with higher heart rates (Chi square p value <0.001).


121 Patients undergoing CTCA
HR >60bpm
n=75
HR ≤60bpm
n=46
Scanned
ORAL VERAPAMIL
n=4
ORAL METOPROLOL
n=71
HR >60bpm
n=4
HR >60bpm
n=12
HR ≤60bpm
n=59
IV VERAPAMIL
n=4
IV METOPROLOL
n=12
Scanned
Scanned
Scanned

3.7 Discussion

An effective heart rate control protocol for use during CTCA scanning in the outpatient setting has been demonstrated. My data confirm the importance of heart rate control for reducing motion artefact and improving image quality. Given the numbers in my study it is difficult to draw conclusions on safety but there were no significant adverse events in this cohort. The study is limited by not being randomised against placebo group for comparison.

Oral beta-blockers were effective in the majority of patients and are the drugs of choice for rate control, verapamil being largely ineffective in the present study. There is a clear need for alternative rate lowering drugs in patients in whom beta-blockers are contra-indicated, and the potential role of ivabradine merits further study.[244]. Intravenous administration of metoprolol provided little additional rate reduction in the minority of patients in whom oral treatment was ineffective.

The question of how to deal with patients who do not respond to the full regime of oral followed by intravenous beta-blockers remains unanswered but a clinical decision needs to be made about the likelihood of obtaining a diagnostic scan set against the risk of unnecessary radiation exposure. My preferred strategy in these patients is to re-book the CTCA scan at a later date when an anxiolytic such as diazepam is given in addition to the metoprolol. In the review of rate control strategies undertaken earlier, it was noted that oral lorazepam was used at one centre as an adjunct to scanning in some patients. An alternative strategy is to gradually up-titrate the dose of beta-blockers over several weeks prior to attendance for the scan. A third strategy, is to administer higher doses of IV metoprolol (up to 30mg) but the safety and efficacy of all these strategies is unknown and further research is needed given the rapidly increasing clinical application of cardiac CT.

Pannu[245] retrospectively reviewed the medications received by 123 patients given rate control medication prior to undergoing CTCA. It is hard to draw many conclusions from this data because of the apparently varied approaches taken, but it appears that a lower dose of oral metoprolol of 50mg was used in the majority of patients and

those that went on to have IV metoprolol had all only received 50mg of oral metoprolol.

In the study by de Graaf,[246] a regime using 50-100mg of oral metoprolol (and in 4% of patients an additional 1mg oral lorazepam) was assessed. In patients in whom beta blockers were contra-indicated the image quality was worse as no alternative rate lowering regime was employed. Of those patients receiving the 'optimal' oral metoprolol strategy (50-100mg metoprolol dependant on initial heart rate) 27% did not achieve the target heart rate of <65bpm.

Maffei[247] retrospectively analysed 560 patients who underwent CTCA and grouped them to various startegies of oral metoprolol, intravenous atenolol or diltiazem or benzodiazepines. Higher doses of metoprolol appear to have been used (100-200mg) than described elsewhere and 62% of patients received lorazepam. The groups receving oral metoprolol or IV atenolol with or without sublingual nitrates had significant reduction in heart rate but there remained nearly 20% of patients in the treated groups who failed to reach a heart rate under 65bpm.

The regime used by Shapiro[248] was a pure intravenous metoprolol strategy whereby repeated boluses of 5mg metoprolol where administered. It is not entirely clear how quickly the dose was titrated as the paper states that heart rate 'was reassessed every 2 min until a HR of <65 bpm was achieved or a maximum dose of metoprolol 20 mg was administered.' Given the pharmacokinetics discussed earlier such titration regimes should wait at least 10 minutes between boluses before repeating. Only 35% of those given intravenous metoprolol achieved target heart rate of <65bpm. The mean dose of metoprolol was 12±10 mg. When this is compared to the oral doses given in mine and other studies and the approximately 50% bioavailability of oral metoprolol is taken into account it can be seen that this reduction in efficacy could be related to comparative underdosing.

Degertekin[249] examined a protocol combining the use of oral atenolol and intravenous esmolol boluses of 1-2mg/kg doses dependant on heart rate. The strategy appeared to reduce heart rate with only transient bradycardia or hypotension in the majority of

patients, however 126 out of the 500 included patients had heart rates above the target of 65bpm after completing the protocol.

Since undertaking this study, ivabradine has increased in clinical use for angina pectoris and heart failure due to the publication of two significant papers demonstrating a reduction in coronary events in angina patients and hospitalisation in heart failure patients.[250, 251] Guarrici undertook a randomised trial assessing the use of 5 days of oral ivabradine before undergoing CTCA.[252] It was shown that there was a significant reduction in heart rate in the ivabradine group, however this was not compared against a beta blocker but either with or without concomitant administration of oral and intravenous atenolol.

At the European Society of cardiology 2010, the results of a randomised trial of a single intravenous bolus of either 10 or 15mg ivabradine, dependent on heart rate, were presented.[253] This was undertaken in patients in whom beta blockers were contraindicated and target heart rate ≤65bpm was reached in 55% of the treatment arm versus 23% in the placebo arm. This certainly has some promise, however intravenous ivabradine is not yet widely available, is not licensed in the United Kingdom and is ineffective in atrial fibrillation.

It can be seen that there still remains heterogeneity in the use of heart rate reduction protocols for performing CTCA. Taken in the context of other studies, the oral beta blocker regime I describe appears to be efficacious and easy to administer, however there are still a large number of patients that fail to reach target heart rates with beta blockers and furthermore there are a significant number of patients who cannot receive beta blockers due to contraindications. With the advent of yet faster scanners the need for rigorous rate control may diminish but meanwhile more work is needed to determine appropriate regimens for those patients who fail to respond to the oral and IV beta-blocker regime described in this study.

4. CT FOR ASSESSING CORONARY ARTERIES

4.1 Abstract

BACKGROUND

Computed Tomography Coronary Angiography (CTCA) is a technique for imaging coronary arteries with increasing indications in clinical cardiology. It has a high negative predictive value and thus is commonly applied for the exclusion of significant coronary disease in low risk populations.

AIMS

To examine the diagnostic accuracy of 64 slice CTCA in patients with known coronary artery disease (CAD).

METHODS

The diagnostic value of CTCA in unstented arterial segments of patients with suspected angina and known coronary artery disease was evaluated by comparison with invasive coronary angiography.

RESULTS

80 patients underwent CTCA and invasive coronary angiography. 724 coronary arterial segments were available for analysis. The sensitivity and specificity of CTCA for significant (≥ 50%) luminal stenosis was, respectively, 83.3% (95% CI 67.1-92.5%) and 96.7% (95% CI 95.1-97.9%) with a positive predictive value of only 63.5% (95% CI 50.4-75.3%) and a negative predictive value of 98.8% (95% CI 97.7 - 99.5%).

CONCLUSION

CTCA64 is of limited value for assessment of disease severity in high risk patients and its low positive predictive value indicates that it cannot substitute for invasive coronary angiography. Its value for ruling out coronary artery disease in low risk populations, however, is not challenged by my findings.

Introduction

In chapter 1 I examined the technology of CT coronary angiography (CTCA) and looked at the evidence for the accuracy of CT technology. It was seen that as the technology has evolved, particularly with the development of 64 slice scanners the accuracy of the technique has continually increased. There remain some difficulties with the technique, particularly artefact related to motion and calcification. Data from the early adopter centres shows universally excellent negative predictive values and, based on this, the technology is enjoying enthusiastic clinical uptake, particularly for rule out of coronary artery disease in low risk populations.[254] However, studies in which higher risk groups have been included have reported more variable diagnostic value[116, 117, 255] and there is the need for further work in such groups to define potential clinical applications. In this chapter I explore the diagnostic value of CTCA for evaluating significantly diseased arterial segments in patients with known coronary artery disease and in the next chapter I will go on to evaluate CTCA for determining the severity of stent restenosis. Taken together these chapters will provide a platform for the clinical evaluation of CTCA in patients with previous coronary stenting and recurrent chest pain in whom information is needed about stent patency and the progression of native disease.

4.2 Methods

4.2.a Ethics

Ethical Approval for this study was given by East London and the City Research Ethics Committee, Study Ref: 05/q0605/183 on 26th June 2006.

4.2.b Population

All patients attending for invasive coronary angiography or percutaneous coronary intervention with prior coronary stent implantation were screened for inclusion in the

study. Exclusion criteria were the presence of unstable symptoms, renal failure, arrhythmias, asthma, age <40, allergy to intravenous contrast media and women of child bearing age. All patients agreeing to participate underwent CTCA within two weeks prior to their scheduled invasive coronary angiography.

4.2.c Imaging

CTCA was performed using a Siemens Somatom Sensation 64 Slice CT scanner. Patients with a heart rate >60 bpm received oral or intravenous metoprolol before the scan, with the aim of scanning at 60 bpm. 1mg of GTN was administered sublingually immediately prior to scanning. Scan parameters vary with patient characteristics but were in the order of: 0.6 mm detector collimation, rotation time 330ms; tube voltage 120 kV; 900 mAs. All scans were performed using retrospective gating without beam modulation. Optimal reconstruction time point at (e.g.) 600ms of cardiac cycle was chosen with the use of preview series. For evaluation of coronary arteries two data sets were reconstructed; the first using the B46f algorithm, slice width 0.6mm and increment 0.2mm and the second with the B35f algorithm, 0.75mm slice width and 0.4mm increment.

Two radiologists, blinded to the results of the invasive angiography reviewed the CTCA images independently using Siemens Circulation software to generate axial images, oblique multiplanar reformatted images and curved multiplanar reformatted images. A segmental scoring developed by the American Heart Association (see Figure 19) was applied and a total of 724 segments were predefined and graded as significantly diseased (≥50% luminal narrowing) or unobstructed (<50% luminal narrowing). Vessels that could not be classified, due for example to excessive artefact, were classified as non-assessable and excluded. Disagreement about lesion severity was resolved by consensus.

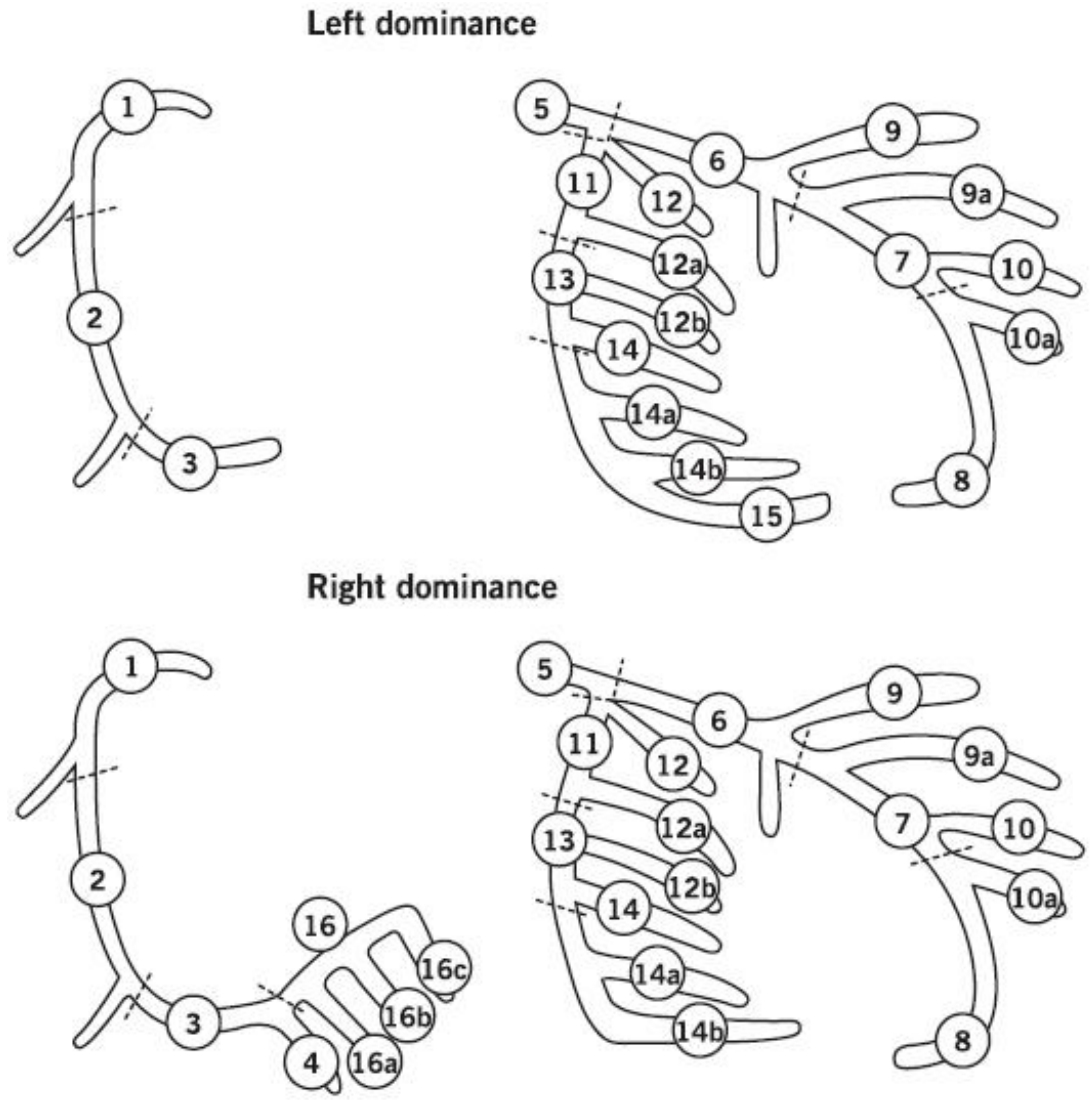


Figure 19 AHA Coronary tree classification system

Invasive cardiac catheterisation (CAX) was performed using standard protocols with a minimum of 6 views of the left coronary system and 2 of the right. The invasive coronary angiograms were reported independently by two cardiologists blinded to results of CTCA or IVUS. The same segmental scoring system (see Figure 19) was used and again disagreement was resolved by consensus.

4.2.d Statistical methods

For the baseline characteristics continuous variables were presented as mean with standard deviation. To compare the diagnostic performance of CAX and CTCA sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated with binomial confidence intervals from a 2x2 table, assuming CAX showed the true disease status. Previously stented segments were excluded from analysis. Tables show true positives (stenoses correctly identified as stenoses), false negatives (unrecognised stenoses), false positives (normal but identified as stenosed) and true negatives (correctly identified as normal). Sensitivity of CAX/CTCA is the proportion of stenoses correctly identified, whereas specificity is the proportion of non-stenosed arteries correctly identified. PPV and NPV are the proportions of correctly identified test positives and test negatives. Stata 8 (version 8.2, StataCorp, College Station, Tex) was used for all analyses in this study.

4.3 Results

4.3.a Patients

There were 80 patients with 724 vessel segments available for analysis. Stented segments were not analysed in the present study.

Table 17 Patient baseline characteristics

Patients	***All patients (n=80)*** ***N (%) or Mean ±SD***
Age	63 ±10
Female sex	13 (16%)
Previous MI	36 (45%)
Previous CABG	9 (11%)
Diabetes	14 (18%)
Smoking history	49 (61%)
Hypertension	56 (70%)
Hypercholesterolemia	69 (86%)
BMI *	28 ±4.1
Drugs	
CAB	16 (20%)
BB	63 (79%)
ACE	68 (85%)
Aspirin	79 (99%)
Statins	75 (94%)
Clopidrogel	54 (68%)

Of 724 native coronary arterial segments, 681 (94.1%) were unobstructed (<50% luminal narrowing), while the remainder (n=43) had significant disease with ≥50% luminal narrowing. CTCA correctly identified 99% of all normal or minimally diseased segments, with a specificity of 96.7% (95% confidence interval 95.1 – 97.9%) and a negative predictive value of 98.8% (95% confidence interval 97.7 - 99.5%). The diagnostic sensitivity of CTCA for significant luminal stenosis was 83.3% (95% confidence interval (67.1-92.5%) and positive predictive value of 63.5% (95% confidence interval 50.4-75.3%).

Table 18 Diagnostic value of CT coronary angiography for native vessel stenosis (≥50% luminal narrowing) in 724 vessel segments in 80 patients compared with invasive coronary angiography.

	CT Angiography vs Coronary Angiography for Native Vessel Assessment					
CT / Angio	Severe disease (≥50% luminal narrowing)	Widely patent (<50% luminal narrowing)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Severe disease (n=43 segments)	40 (93%)	3 (7%)	83.3 (67.1 – 92.5)	96.7 (95.1 – 97.9)	63.5 (50.4 – 75.3)	98.8 (97.7 - 99.5)
Widely patent (n=681 segments)	8 (1%)	673 (99%)				

*true abnormal diagnosis defined as stenosis >=50% lumen loss or >=50% luminal narrowing of native vessel according to coronary angiography

4.4 Discussion

In the present study I have shown that 64 slice CTCA in patients with recurrent symptoms after coronary stenting has a rather low sensitivity for significant disease in unstented segments of the coronary arteries but, as in low risk populations, it provides reliable rule out of disease in unobstructed segments. Clinically, however, the questions to be answered in these patients with recurrent symptoms after stenting are 1) is progressive disease present in the native circulation or 2) is there restenosis within the stent? My study shows that the first of these questions cannot reliably be answered by CTCA64 and the fact that unobstructed segments are correctly identified in >95% of cases does not alter the fact that the clinical role of CTCA64 in these high risk patients is very limited.

It is important to emphasise that mine was a different group of patients from those in which the diagnostic value of CTCA has previously been evaluated. I included only patients with known coronary artery disease who had undergone prior coronary intervention. This contrasts with the lower risk patients included in many of the earlier published studies and differs from the clinical application for which CTCA is most often used; that is in the exclusion of coronary disease in patients with low probability of coronary disease.

There have been three multicentre studies looking at 64 slice CTCA for assessment of native coronaries compared with invasive coronary angiography (Table 19). These are particularly relevant to my study because all were performed in patients with a high (50-100%) prevalence of coronary artery disease and all showed diagnostic accuracy that falls short of clinical requirements. Importantly, the positive predictive values for significant (≥50%) coronary artery disease in two of these studies was less than 60% and almost identical to the value I report in this chapter. In the third study by Miller[255] the positive predictive value of CTCA64 was 82% which, although somewhat higher, is scarcely sufficient for diagnostic purposes. Taken together with the work I report in

this thesis, it is clear that in high risk patients, CTCA64 is of limited value for assessment of disease severity and cannot substitute for invasive coronary angiography. Its value for ruling out coronary artery disease in low risk populations, however, is not challenged by my findings.

Table 19 Multicentre studies of 64 slice CTCA

	Sesnitivity	Specificity	PPV	NPV
Budoff 2008[117]	84 (74-91)	90 (88-92)	51 (43-59)	99 (98-99)
Miller 2008[255]	75 (69-81)	93 (90-94)	82 (77-86)	89 (86-92)
Meijboom 2008[116]	95 (92-97)	77 (74-80)	59 (55-63)	98 (96-99)

4.4.a Strengths and Limitations

The key strength of this study is that it enrolled a well-defined high risk group of patients, all of whom were known to have previously treated coronary artery disease. A key weakness is that I did not record data in such a way that the interobserver variability could be reported which would have been a useful parameter in considering the utility of the technique in clinical practice. Nevertheless, the similarity of my findings to those reported in larger multicentre studies indicates that reporting quality was unlikely to have been substantially different.

4.4.b Conclusion

This study shows that CTCA with a 64 slice CT scanner has a rather low positive predictive value for quantifying the severity of coronary artery disease in high risk populations. All my patients had prior coronary stenting and in the next chapter the value of CTCA for assessing stent restenosis will be reported.

5. CT FOR ASSESSING CORONARY ARTERY STENTS

5.1 Abstract

OBJECTIVES

To compare the assessment of coronary stents by computed tomography coronary angiography CTCA, invasive coronary angiography and intravascular ultrasound.

BACKGROUND

Angiographic assessment of coronary stents is difficult because the arterial lumen is variably obscured by metallic struts. Studies using CTCA have reported limited diagnostic value for stent restenosis but the comparator has been invasive coronary angiography.

METHODS

We used intravascular ultrasound (IVUS) to define restenosis within stented segments of coronary arteries and compared the findings with 64 slice CTCA and invasive coronary angiography. Treating every stent as an observation (overlapping stents counted as one) and adjusting for independent observations between patients there were 80 patients with 125 stented segments available for analysis. Forty-eight patients had additional IVUS examination of 69 stented segments.

RESULTS

Using IVUS as the gold-standard for stent restenosis (minimal lumen diameter <50% proximal and distal reference diameters) CTCA and invasive coronary angiography had comparable diagnostic specificities for binary stent restenosis: 82.7% (95% confidence intervals(CI) 69.7-91.84%) and 78.9% (95% CI 65.3-88.9%), respectively. Sensitivities were lower, particularly the sensitivity of CTCA which was only 11.8% (95% CI 1.5-36.4%) compared with 58.8% (95% CI 32.9-81.6%) for invasive coronary angiography. However, when the diagnostic value of CTCA was tested against the invasive angiographic gold standard specificity increased to 90.1% (95% CI 81.5-95.6%) but sensitivity remained low at 29.6% (95% CI 16.8-45.2%).

CONCLUSION

Angiographic evaluation of coronary stents, whether by CTCA or invasive angiography, commonly yields false negative diagnosis of binary restenosis. Future evaluation of

new technologies should use IVUS or other imaging comparators with a more robust diagnostic performance.

5.2 Introduction

Coronary stents are frequently deployed in the treatment of coronary artery disease. Despite advances in technology with increasing use of drug eluting stents, a significant number of patients will develop restenosis in coronary stents. There is also a significant number of patients returning with chest pain post stent implantation who are later shown to have no evidence of in stent restenosis.

In Chapter 1 the current techniques for assessing in stent restenosis were examined, the mainstay of which is invasive coronary angiography (CAX) supplemented by intravascular ultrasound (IVUS). With the increasing volume of stent procedures now being undertaken, angiography for suspected restenosis represents a substantial part of an interventional laboratory's workload. In our own centre about 30% of all diagnostic procedures are in patients who had previously undergone coronary stenting. Computed tomography coronary angiography (CTCA) has the advantage of being a non-invasive technique that allows visualisation of the coronary arteries. In Chapter 4 I assessed the accuracy of CTCA compared with CAX in native coronaries and showed that its positive predictive value is low at 63.5%, as has also been found in other studies. Nevertheless, in symptomatic patients who have undergone coronary stenting, the value of CTCA for assessing restenosis is also relevant, even though stents pose a unique challenge for CT technology. This is due to a combination of the factors that affect assessment of all coronary arteries (motion artefact and limits in spatial resolution) and also the particular artefacts due to the dense stent material and their small size.

As early as 1994[256] electron beam computed tomography (EBCT) was used to identify the location of early Palmaz-Schatz stents in the coronary arteries. As has been discussed earlier EBCT is a technique that sends a steered beam of electrons at the area of interest achieving a high temporal resolution but a low spatial resolution, such that it cannot visualise accurately the lumen within a stent. An alternative approach, therefore, has to be used to assess flow of contrast to the coronary artery beyond stented segments.

Three studies used a similar methodology to evaluate stent patency in the following manner. Initially a static non-contrast scan was used to locate the stents and then an area of interest was selected distal to the stent within the artery and repeat scans were performed at this level during the injection of peripheral intravenous contrast medium. From these images a cine of contrast filling distal to the stent and a time density curve of contrast enhancement distal to the stent can be obtained.

Schmermund[257] reported a small series of patients who underwent EBCT after coronary stent placement and reported that there was some scope for assessing for stent occlusions by EBCT by examining contrast flow beyond the stent but that it was not possible to comment on other degrees of restenosis within the stent.

Pump[258] attempted to assess 321 stents in 202 patients; artefacts and technical problems excluded 4% of vessels. 96% of stented vessels could be assessed by visual cine loop assessment but only 53% of vessels could be assessed by time density curve. Only 23 of the assessed stented segments were significantly stenosed on invasive coronary angiographic assessment. The results were compared with invasive coronary angiography and a sensitivity of 78%, specificity of 98% with a positive predictive value of 82% and negative predictive value of 97% were reported.

In 2003 Knollam[259] undertook EBCT on 117 patients in the above manner and these results were then compared to invasive coronary angiography. No correlation was found between the visual assessment and invasive coronary angiographic findings. There was a correlation between the time to peak contrast density beyond the stent but the optimal threshold yielded a sensitivity of 72% and specificity of 60%. Knollman also unsuccessfully attempted assessment by visual evaluation of stent lumen patency. EBCT gradually fell out of clinical use as MSCT became more widespread and attention turned to the new MSCT scanners as a potential means of assessing coronary stents.

Nieman[260] investigated a number of stents in vitro, in a model that excluded cardiac motion using 4x1mm and 2x0.5mm collimator arrangements. It was shown that the high density of the stent material made them appear much larger than they were and a combination of beam hardening and partial voluming artefacts resulted in a higher

average CT density within the stent lumen and only a small area of the lumen remained free of artefact.

Beam hardening artefacts are caused by the loss of lower energy photons from the X-ray beam as it passes through an object, resulting in an increase in mean energy. This can result in streak artefacts or cupping where an object of uniform density appears less dense in its centre. Partial voluming artefacts occur when dense objects such as coronary stents that are off centre protrude partially into the x-ray beam. Due to divergence of the x-ray beam the beam has a different width when the off centre object is scanned from different directions as the tube rotates. From some angles the beam will be wide enough to include the object and from other angles the beam will be narrower and thus not include the object. The inconsistencies between the views can cause shading artefacts to appear.[261]

Numerous post-processing algorithms have been developed by CT manufacturers to counter some of these problems. One particular technique that was employed in my centre to optimise stent visualisation was the use of a sharper reconstruction algorithm for stent assessment, which although it can increase noise levels within images, reduces the blooming artefact caused by both stents and calcification. The increased image noise often means higher X-ray output (mAs) is used to overcome this and thus results in potentially higher patient radiation doses.

Kruger[262] used a scanner with 4 x 1mm collimation and a rotation time of 500ms to investigate 32 stents in the native coronary arteries of 20 patients, excluding patients with CABG and arrhythmias. It was not possible to visualise any of the lumen within the stents, but they did comment on a lack of contrast beyond two stents that matched with occluded stents demonstrated by invasive coronary angiography.

Cademartiri [263] assessed 47 stents in 42 patients using Siemens Sensation 16 slice scanner. This scanner has a rotation time of 420ms and collimation was 16x0.75mm slices. Only patients with one stent in the native coronary tree, under the age of 70, in sinus rhythm with a heart rate less than 65 bpm were included. The stents were assessed for the presence of stenosis ≥50% and this was compared with contemporaneous invasive coronary angiography assessment. It was demonstrated

that MSCT had a sensitivity of 50% (95% CI 19-81%), specificity of 100% and positive predictive value of 100% and negative predictive value of 88% (95% CI 73-98%).

Cademartiri published a second study[264] of 76 stents in 51 patients performed in the same manner on the same scanner with results compared to invasive coronary angiography. Sensitivity was 83.3% (95% C.I. 35.9 – 99.6%), specificity 98.5% (95% C.I. 92.1-100%), positive predictive value 83.3% (95% C.I. 35.9-99.6%) and negative predictive value 98.5% (95% C.I. 92.1 to 100%).

A further study using 16 slice MDCT[265] assessed 42 stents in 31 patients, all in sinus rhythm using a scanner with 16x0.75mm collimation and 420ms rotation time. It was shown that smaller stents had greater degrees of artefact and 7 stents were excluded from analysis because of poor image quality. Separate results were reported for two readers of CT and comparing all the included stents with invasive coronary angiography the sensitivity of MDCT for evaluating stent patency was 83% (reader 1) and 100% (reader 2), specificity was 90% (reader 1) and 93% (reader 2), positive predictive value was 63% (reader 1) and 75% (reader 2), and negative predictive value was 96% (reader1) and 100% (reader 2).

The left main coronary artery is often the largest area in the coronary tree as it bifurcates and gives rise to the left anterior and left circumflex arteries that supply a large area of myocardium. Thus, when stenting of the left main coronary artery is undertaken it is likely that larger stents will be used. Given that some of the artefacts in coronary stent CTCA are exacerbated by the small size of the stents it is possible that CTCA is more reliable in these larger stents. Given the importance of the left main coronary artery and the severe consequence of occlusion of this vessel, there has been a suggestion that all left main coronary artery stents undergo repeat angiography at an interval of 1-6 months post stent implant although lately this is falling out of practice.[266] There would therefore be an even greater desire to find a less invasive means to assess these stents. Gilard[267] investigated 16 slice MDCT in 29 patients from this subgroup with a mean stent diameter of 3.9mm. The scanner used had 16x0.75mm collimation and a rotation time of 420ms and patients with arrhythmias were excluded. CTCA result was compared with invasive coronary angiography for

stenoses >50%. Two stents could not be analysed due to excessive calcification in the left main stem, but all other stents were correctly graded giving a sensitivity of 100%, a specificity of 92% and positive predictive value of 100% and negative predictive value of 92%. This would support the supposition that stents in the left main stem can be more reliably assessed by CTCA.

Gaspar[268] investigated 111 stents in 65 patients using a 40 slice scanner with 40 x 0.625 mm collimation and gantry rotation speed of 420ms. Using both >50% restenosis and >60% restenosis cut-offs and comparing with invasive coronary angiography, poor sensitivity and specificity were found, although a negative predictive value of 97.4% (95% CI 93.8–100%) was found when using a >60% restenosis definition.

Evidence from phantom studies[269-271] have shown that 64 slice scanners are likely to better visualise stents with less artificial narrowing of the lumen due to artefact.

Rist[272] studied a small number of patients using a 64 slice scanner with 64 x 0.6 mm collimation and rotation time of 330ms. In this promising pilot study compared with invasive coronary angiography consensus readings for in stent re-stenosis gave a sensitivity of 75%, specificity of 92%, positive predictive value of 67% and negative predictive value of 94%.

In the in vivo studies described above, invasive coronary angiography was used as the gold standard to which CTCA was compared. However, as has been explored in Chapter 1, invasive angiography is a flawed gold standard due to its planar nature and inability to visualise coronary plaque in relation to stent struts, and a more accurate gold standard for this purpose is intravascular ultrasonography (IVUS).

Intravascular ultrasonography has a spatial resolution far greater than that of conventional invasive angiography. Furthermore, invasive angiography which provides two-dimensional representations of the coronary arteries cannot fully reveal the nature of three-dimensional plaque and the angiographic view can be obscured by overlapping vessels. IVUS can be used to provide detailed visualisation of stents, stent apposition to vessel wall and the presence of neo intimal hyperplasia. IVUS is now often used as the gold standard for assessing in stent restenosis and hyperplasia,

particularly when comparing different coronary stents. In stent restenosis is often seen as very short segments of stenosis (<1mm)[48] which can be missed by conventional angiography. The IVUS probe within the vessel is more likely to detect the area of most narrowing. Angiography only allows a measurement in variations of luminal diameter of stented and adjacent non-stented areas and provides only an indirect measure of in-stent neointimal hyperplasia and cannot account for positive remodelling.[49]

In this study CTCA and conventional invasive angiography are evaluated against the gold standard IVUS assessment for stents.

5.3 Methods

5.3.a Ethics

Ethical Approval for this study was given by East London and the City Research Ethics Committee, Study Ref: 05/q0605/183 on 26th June 2006.

5.3.b Population

All patients attending for invasive coronary angiography or percutaneous coronary intervention with prior coronary stent implantation were screened for inclusion in the study. Exclusion criteria were the presence of unstable symptoms, renal failure, arrhythmias, asthma, age <40, allergy to intravenous contrast media and women of child bearing age. All patients agreeing to participate underwent CTCA within two weeks prior to their scheduled invasive angiography. A subgroup of patients was also assessed using intravascular ultrasound to determine the minimum luminal area and percentage stenosis of stents except where the lumen was too small to pass the IVUS probe.

5.3.c Imaging

CTCA was performed using a Siemens Somatom Sensation 64 Slice CT scanner. Patients with a heart rate >60 bpm received oral or intravenous metoprolol before the scan, with the aim of scanning at 60 bpm. 1mg of GTN was administered sublingually immediately prior to scanning. Scan parameters vary with patient characteristics but were in the order of: 0.6 mm detector collimation, rotation time 330ms; tube voltage 120 kV; 900 mAs. All scans were performed using retrospective gating without beam modulation. Optimal reconstruction time point at (e.g.) 600ms of cardiac cycle was chosen with the use of preview series. For evaluation of stents two data sets were reconstructed; the first using the B46f algorithm, slice width 0.6mm and increment 0.2mm and the second with the B35f algorithm, 0.75mm slice width and 0.4mm increment.

Images were reviewed using axial images, oblique multiplanar reformatted images and curved multiplanar reformatted images using the Siemens Circulation software. Two radiologists, blinded to the results of the invasive angiography or IVUS independently reviewed the images and, in cases of disagreement, a consensus result was recorded. The degree of in-stent restenosis was defined in a binary manner as being <50% stenosis or stenosis ≥50% including complete occlusions. Stents that were unable to be classified, due for example to excessive artefact, were classified as non-assessable and excluded.

Cardiac catheterisation was performed using standard protocols with a minimum of 6 views of the left coronary system and 2 of the right. Angiograms were analyzed independently by two cardiologists blinded to the results of CTCA or IVUS. In cases of disagreement a consensus result was recorded. Again, a binary classification was used for stent restenosis

Intravascular ultrasound was performed on any accessible stents using a Volcano In-Vision Gold system with a 20Mhz Eagle Eye Gold IVUS probe and a R200 automated pullback device at 0.5mm/s and data saved in DICOM format for analysis. These data were analysed by a cardiologist blinded to the results of the CTCA or invasive

angiography. Percentage stenosis was calculated using proximal and distal reference areas compared to the minimal lumen area. Where the distal reference area was larger than the proximal, the vessel was assumed not to taper and the distal reference was used to calculate stenosis severity. When the distal reference area was smaller than the proximal area the vessel was assumed to taper in a linear fashion and the predicted vessel area was calculated at the point of maximal stenosis. These data were then recorded in a binary fashion in a similar manner to the data from CT and CAX.

5.3.d Statistical methods

For the baseline characteristics continuous variables were presented as mean with standard deviation. To compare the diagnostic performance of CAX and CTCA with IVUS sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated with binomial confidence intervals from a 2x2 table, assuming IVUS showed the true disease status. Tables show true positives (stenoses correctly identified as stenoses), false negatives (unrecognised stenoses), false positives (normal but identified as stenosed) and true negatives (correctly identified as normal). Sensitivity of CAX/CTCA is the proportion of stenoses correctly identified, whereas specificity is the proportion of normal stents correctly identified. PPV and NPV are the proportions of correctly identified test positives and test negatives. Stata 8 (version 8.2, StataCorp, College Station, Tex) was used for all analyses in this study.

5.4 Results

There were 80 patients with 125 stented segments available for analysis. Forty-eight patients had additional IVUS examination of 69 stented segments. These 69 stented segments included 111 stents and the characteristics of these stents are detailed in

Table 21. I compared the results between IVUS, CTCA and invasive angiography in these 69 segments.

Table 20 Patient baseline characteristics

Patients	***Patients with IVUS (n=48)*** ***N (%) or Mean ±SD***	***All patients (n=80)*** ***N (%) or Mean ±SD***
Age	62 ±10	63 ±10
Female sex	9 (19%)	13 (16%)
Previous MI	24 (50%)	36 (45%)
Previous CABG	5 (10%)	9 (11%)
Diabetes	7 (15%)	14 (18%)
Smoking history	31 (65%)	49 (61%)
Hypertension	31 (65%)	56 (70%)
Hypercholesterolemia	40 (83%)	69 (86%)
BMI	27 ±3.8	28 ±4.1
Drugs		
Ca channel blocker	9 (19%)	16 (20%)
BB	36 (75%)	63 (79%)
ACE	40 (83%)	68 (85%)
Aspirin	48 (100%)	79 (99%)
Statins	45 (94%)	75 (94%)
Clopidrogel	33 (69%)	54 (68%)
Stents		
LMS	10 (14%)	12 (7%)
LAD	11 (11%)	61 (37%)
Circumflex	18 (18%)	24 (14%)
RCA	32 (32%)	54 (32%)
Others: Intermediate artery	1 (1%)	3 (2%)
Diameter (mm)	3 ±0.5	3 ±0.5
Length (mm)	18 ±6.1	18 ±6.1

Table 21 Stent characteristics

	Stents with characteristic (n=111) ***n (%) or Mean ±SD***
Implant Location	
Right coronary artery	38 (34%)
Left main stem	11 (10%)
Left anterior descending	40 (36%)
Left Circumflex	20 (18%)
Intermediate	2 (2%)
Stent Type	
Taxus	19 (17%)
Liberte	16 (14%)
Cypher	17 (15%)
Velocity	2 (2%)
Driver	12 (11%)
Endeavour	3 (3%)
Crossflex	4 (4%)
Zeta	4 (4%)
Sonic	3 (3%)
Other/Unknown	31 (28%)
Time from implant	27 months ± 27months
Stent Size	
Diameter (mm)	3 ±0.5
Length (mm)	18 ±6.1

5.4.a IVUS comparator

The diagnostic performance of CTCA and Invasive coronary angiography for stent restenosis compared with the IVUS gold standard is summarised in Table 22. IVUS examination of the 69 stented segments showed that 52 were normal or minimally re-stenosed, while the remainder (n=17) had severe restenosis with ≥50% luminal narrowing. The CTCA examination correctly identified 43 (83%) of the normal or minimally re-stenosed stented segments but only 2 (12%) of the segments with ≥50% restenosis. Invasive coronary angiography in the same patients correctly identified 41 (79%) of the normal or minimally re-stenosed stented segments and 10 (59%) of the segments with ≥50% restenosis. Comparison of diagnostic value showed that the specificities of CTCA (82.7% (95% confidence intervals 69.7-91.84%)) and invasive coronary angiography (78.9% (95% confidence intervals 65.3-88.9%)) for binary stent restenosis were comparable. Sensitivities were lower, particularly the sensitivity of CTCA which was only 11.8% (95% confidence intervals 1.5-36.4%) compared with 58.8% (95% confidence intervals 32.9-81.6%) for invasive coronary angiography. Inclusion of the 2 patients with complete stent occlusions by invasive coronary angiography, both of which were correctly identified by CTCA, increased the diagnostic sensitivities to 21% for CTCA and 63% for invasive angiography, respectively.

5.4.b Invasive coronary angiography comparator

Diagnostic performance of CTCA for stent restenosis using invasive coronary angiography as gold standard is summarised in Table 23. Invasive coronary angiography identified 104 of the 125 stents as normal or minimally re-stenosed and 21 stents as re-stenosed with ≥50% luminal narrowing, including 2 with complete occlusion. The diagnostic value of CTCA using invasive angiography as the comparator showed that specificity was 90.1% (95% confidence intervals 81.5-95.6%) but sensitivity was only 29.6% (95% confidence intervals 16.8-45.2%).

Table 22 IVUS gold standard: diagnostic value of CT and invasive coronary angiography for stent restenosis (IVUS: ≥50% luminal narrowing) measuring 69 stents in 48 patients. True abnormal diagnosis defined as restenosis >=50% lumen loss according to IVUS.

	CT Angiography vs IVUS for Stent Assessment					
CT / IVUS	Restenosis (≥50% lumen loss)	No restenosis (<50% lumen loss)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Restenosis (n=17 stents)	2 (12%)	15 (88%)	11.8 (1.5 – 36.4)	82.7 (69.7 – 91.8)	18.2 (9.1 - 61.4)	74.1 (61.9 – 84.7)
No restenosis (n=52 stents)	9 (17%)	43 (83%)				
	Invasive Coronary Angiography vs IVUS for Stent Assessment					
Angio / IVUS	Restenosis (≥50% lumen loss)	No restenosis (<50% lumen loss)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Restenosis (n=17 stents)	10 (59%)	7 (41%)	58.8 (32.9 – 81.6)	78.9 (65.3 – 88.9)	47.6 (25.7 – 70.2)	85.4 (72.2 – 93.9)
No restenosis (n=52 stents)	11 (21%)	41 (79%)				

Table 23 Diagnostic value of CT coronary angiography for in-stent restenosis and native vessel stenosis (≥50% luminal narrowing) measuring 125 stents in 80 patients when invasive coronary angiography taken as gold standard. True abnormal diagnosis defined as restenosis >=50% lumen loss or >=50% luminal narrowing of native vessel according to coronary angiography.

	CT Coronary Angiography vs Invasive Coronary Angiography for Stent Assessment					
CT / Angio	Restenosis (≥50% lumen loss)	No restenosis (<50% lumen loss)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Restenosis (n=21 stents)	13 (62%)	8 (38%)	29.6 (16.8 – 45.2)	90.1 (81.5 – 95.6)	61.9 (38.4 - 81.9)	70.2 (60.4 – 78.8)
No restenosis (n=104 stents)	31 (30%)	73 (70%)				

5.5 Discussion

5.5.a What is already known

Previous studies have shown that the diagnostic performance of CTCA with 64 slice scanners for stent assessment is inadequate, many cases of significant restenosis being missed due to low diagnostic sensitivity.[273-275]

Negative predictive value appears higher and the use of CTCA for rule out of restenosis has been suggested by some investigators[276] similar to its growing role for rule out of native coronary artery disease in patients with a low probability of disease. The majority of these studies, however, have used invasive coronary angiography as the comparator which may not itself provide reliable diagnostic information about luminal obstructions within coronary stents.

5.5.b Comparison with other studies

Since commencing this study there have been further studies published investigating the role of 64 slice CTCA in native coronary arteries and in stented arteries.

Rixe[273] used a 64 slice scanner with 64x0.6mm collimation and rotation time of 330ms to assess in stent restenosis compared with invasive angiography. Only 58% of all stents were classed as evaluable by MDCT and excluding non-evaluable stents the sensitivity was 86% (95% CI 42-99%), specificity 98% (95% CI 88-100%), positive predictive value 86% (95%CI 42-99%) and negative predictive value 98% (95%CI 88-100%).

Van Mieghem[277] used IVUS as the gold standard in a study using 64 slice CT. Over 83% of the stents in their study were left main coronary artery stents and there were only 11 stents with sufficient restenosis to compare IVUS and CTCA for in stent restenosis and there was only a moderate correlation between CTCA and IVUS for diameter and area restenosis.

Ehara[274] used a 64 slice scanner with 64 x 0.6mm collimation and rotation time of 330ms to assess 125 stented lesions in 81 patients compared with invasive coronary angiography. When including unassessable segments, sensitivity was 92% (95% CI 81-100%), specificity was 81% (95% CI 74-89%), positive predictive value was 54% (95% CI 39-69%), and negative predictive value was 98% (95% CI 95-100%).

Cademartiri[275] again used invasive coronary angiography as a gold standard and two different 64 slice scanners were used with 64x0.6mm collimation and rotation time of 330ms and 64x0.5mm collimation and 400ms rotation time. Stents <2.5mm diameter were excluded and 7.3% of stents were excluded due to artefact. It was shown that sensitivity, specificity, and positive and negative predictive value to detect significant in-stent restenosis were 95.0% (95% CI 85-100%), 93.0% (95% CI 90-97%), 63.3% (95% CI 46-81%), and 99.3% (95% CI 98-100%). The superior results in this study cannot be attributed to the improved spatial resolution of the 64x0.5mm scanner as only 32 patients were scanned on this scanner compared with 150 on the 64x0.6mm scanner.

5.5.c What this study adds

It is not clear whether the under-performance of CTCA compared with invasive coronary angiography for stent assessment is the result only of technical inferiority in visualising the stent lumen or whether it is an artefact of an imperfect comparator. This study suggests that invasive coronary angiography is indeed an imperfect comparator for assessing the patency of coronary stents by showing that when CTCA is compared with intravascular ultrasound (IVUS) its performance remains sub-optimal for diagnostic purposes but is only little worse than the performance of invasive coronary angiography. The difficulties of stent assessment by invasive coronary angiography have been previously reported[35-40] but my study shows how these can undermine the value of invasive coronary angiography as a comparator for evaluating emerging technologies. In contrast, IVUS provides direct visualisation of the internal stent lumen allowing more precise assessment of intimal hyperplasia and restenosis against which to judge the diagnostic value of CTCA. The pick-up rate for stent restenosis by CTCA and invasive angiography was low in comparison with previous

studies, but this no doubt reflects the fact that stent occlusions - reliably detected by angiography - were excluded because IVUS examination was impossible. This study also includes a more clinically realistic unrestricted cohort including older stent designs with larger strut thickness with over 55% of identified stents having a strut thickness greater than 100µm. These thicker stent struts are more prone to blooming artefact by CT and are thus likely to be less reliably assessed by CTCA and this could contribute to the lower sensitivities and specificities compared with other studies. [278] Nevertheless, my conclusions concerning stent assessment by CTCA are likely to be robust because the analysis comparing it with the conventional invasive angiographic gold-standard, confirmed a diagnostic performance similar to that reported by previous investigators.[116, 117, 279]

5.5.d Strengths and limitations

An important strength of this study was the near contemporaneous assessments of stent patency by 3 separate technologies in 48 patients. The study covered a more realistic clinical range of patients with a variety of stent types and stenting techniques implanted over a wide timescale prior to assessment. The study was limited by having to exclude patients with the most severe stenoses and complete stent occlusions from IVUS analysis since the probe cannot be passed in these cases. It is certain that the diagnostic value of CTCA64 would have been greater had such patients been included since coronary obstructions are reliably identified by CTCA64. It would have been useful to assess individual readers assessment for each modality allowing calculation of interobserver variability which is an important parameter when considering the reproducibility and applicability of a diagnostic modality. There continue to be further advances in CT technology, with increase in coverage and temporal resolution likely to reduce artefact, however there has, as yet been no major improvement in spatial resolution which will be necessary to allow more accurate assessment of stents and in stent restenosis.[280-282] The use of iterative reconstruction is likely to see improvements in stent assessibility even with the same scanner technology due to reduction in noise

and reduced blooming artefact and stent evalution will need to continually be re-evaluated as the technological capabilities continue to improve.

5.5.e Conclusions

CTCA64 cannot provide the diagnostic performance required clinically for assessing stent restenosis. Thus in patients with recurrent angina after coronary stenting neither the progression of native disease nor the severity of stent restenosis can be reliably assessed using CTCA64. The recommendation based on the work I have presented in the last two chapters, therefore, is that these patients are assessed by invasive coronary angiography with additional ischaemia testing or IVUS evaluation of the stent lumen as necessary.

6. CTCA AS AN ENDPOINT FOR EVALUATION OF BIOMARKERS IN STABLE CORONARY ARTERY DISEASE

6.1 Abstract

BACKGROUND

Computed Tomography Coronary Angiography (CTCA) is a technique for imaging coronary arteries with increasing indications in clinical cardiology with potential utility as an endpoint in clinical research.

AIMS

To demonstrate utility of CTCA as an endpoint in assessment of novel biomarkers.

METHODS

The utility of CTCA for evaluating the diagnostic value of B-type natriuretic peptide (BNP) and high sensitivity cardiac troponin I (hs-TnI) was evaluated by blood sampling in patients with suspected angina before and after exercise.

RESULTS

In 93 patients with suspected angina CTCA provided a useful endpoint for assessing the diagnostic value of novel circulating biomarkers. BNP levels were higher in the 13 patients shown to have significant (≥50% stenosis) coronary artery disease compared with patients who had unobstructed coronary arteries (18.08pg/ml (IQR 22) vs 9.14pg/ml (IQR 12.62), p=0.024) and increased significantly with exercise, particularly in the group with anatomic coronary artery disease (2.73 ± 5.69 pg/ml vs 1.27±3.29 pg/ml, p=0.16). Conversely I found no association between hs-TnI and the presence of CAD.

CONCLUSION

CTCA is a useful non-invasive method for diagnosis of coronary artery disease, with a high sensitivity for rule-out in low risk populations. CTCA also finds application as an endpoint for diagnostic evaluation of novel biomarkers and confirmed an association between BNP and stable coronary artery disease.

6.2 Introduction

As discussed in chapter 1 CTCA has a useful role for diagnosis of coronary artery disease, particularly in populations with a low prevalence of disease in whom it provides a reliable rule-out. It is less useful for determining the severity of disease in higher risk populations as I showed in chapter 4, but even in these patients it can provide a reliable indication of whether the coronary arteries are normal. Its ability to confirm the absence of coronary artery disease noninvasively makes it an attractive test endpoint for novel diagnostic markers.

In Chapter 1 I discussed the well established role of the biomarkers cardiac troponin and B-type natriuretic peptide for the diagnosis of acute coronary syndromes and heart failure. However, both biomarkers may also be elevated in stable ischaemia but this has received little attention from researchers. Indeed, the most recent NICE guideline CG95[283] did not even consider the diagnostic potential of novel biomarkers in patients with suspected angina. The development of high sensitivity troponin assays which lower the detection threshold by a factor of at least six heightens the diagnostic potential of this biomarker in stable coronary disease. However, neither troponins nor BNP have been systematically evaluated for the diagnosis of coronary artery disease in patients attending RACPCs with suspected angina.

In the present study, therefore, I have used CTCA as an endpoint for evaluating the diagnostic value of BNP and hsTnI in patients with recent onset chest pain attending a RACPC.

It was my aim within the setting of the RACPC to assess the utility of the biomarkers cTnI and BNP and both calcium scoring and CTCA for predicting cardiac outcomes in the cohort of patients presenting with stable chest pain of recent onset. The aim was to assess these new techniques in addition to existing clinical assessment and exercise

ECG. The protocol, ethical approval and funding were obtained to allow recruitment of patients from this clinic. All assessments were to be done on site except for the CT coronary angiogram which was to be performed at a separate centre due to the scarcity of the technology at the time, and the generous donation of the facilities for this purpose. The other centre was 12 miles from the recruiting centre, the other side of central London. During recruitment it became clear that the patients were reluctant to travel across London for the CTCA and a large proportion of patients were failing to attend for their scans. This may be partly due to the additional need for time off work in a relatively poor population and the knowledge that the scan would not alter the patients treatment. Thus my initial plan to recruit for a cohort study looking at outcome measures failed to recruit sufficient numbers to be able to provide significant results and thus I present a cross sectional analysis of the data obtained from these patients. A similar issue was found when attempting to assess cTnI levels 24 hours post exercise test with only a very small number of patients returning for repeat blood sampling.

6.3 Methods

6.3.a Ethics

Ethical Approval for this study was given by East London and the City Research Ethics Committee, Study Ref: 06/Q0605/94 on 24th Nov 2006.

6.3.b Inclusion criteria

All patients with undifferentiated chest pain and a high (>80%) or intermediate (20-80%) probability of coronary artery disease based on age, gender and typicality of symptoms.[284] Typicality of symptoms is defined by site (retrosternal, arms, throat), precipitating factors (exercise, cold, emotion), and relieving factors (rest, GTN), chest discomfort with all 3 defining features being classed TYPICAL, any 2 out of 3 ATYPICAL, and only 1 out of 3 NON-SPECIFIC.

6.3.c Exclusion criteria

Women of child−bearing potential, age <40, inability to consent, severe anaemia (Hb <11.0 g/dl), previous history of coronary heart disease (revascularisation, ACS) conditions precluding exercise tolerance test or its interpretation (inability to exercise, left bundle branch block, repolarisation abnormalities, paced rhythm, digoxin therapy etc). Conditions precluding CT coronary angiography (persistent atrial fibrillation, known renal failure with creatinine >160 mmol/l, inability to breathold ≥10secs, and previous allergic reaction to intravenous contrast).

6.3.d Patient recruitment and protocol

All patients attending the RACPC were logged onto a clinical database that included demography, risk factors, examination findings, ECG findings, clinical diagnosis and treatment. Probability of coronary artery disease was generated automatically using Diamond and Forrester estimates,[284] and those patients with high or intermediate probability were invited to participate in the study, having given written and informed

consent. All patients had routine investigation as follows:12 lead ECG, blood sampling (blood count, renal function).

6.3.e Blood sampling

Blood samples were collected after 30min supine rest and 15 minutes after treadmill stress testing into a pre chilled EDTA bottle stored at -80 degrees C for less than 3 months for analysis of biomarker concentration (see below).

6.3.f Treadmill stress testing

All patients underwent symptom-limited treadmill stress testing using the Bruce protocol. The tests were interpreted by a cardiologist as either positive, negative or inconclusive based on ST segment changes.

6.3.g Multi-slice CT scan

This was performed within three weeks of recruitment. Patients received oral or IV metoprolol or verapamil before the scan, with the aim of scanning at (or about) a heart rate of 60 bpm. All patients were scanned on a 64 slice MSCT scanner. Scan parameters were in the order of: 0.75mm collimations; rotation time 0.33s; tube voltage 100 kV; 680 mAs. All scans were performed using retrospective gating with beam modulation with aim of reducing radiation dose. Reconstructed slice width 1mm. Reconstruction time point at (e.g.) 425ms of cardiac cycle (varies according to individual patient). 1-5mm axial and double-oblique MIP and MPR image reconstructions. A test dose of 20 mls. of non-ionic contrast medium to enable timing of the scan with passage of the main contrast volume (e.g. Omnipaque 350, Amersham Health) injected IV at 4ml/s. This was followed by an IV injection of 40mls of normal saline as a ‘chaser’. Calcium scores were obtained using the conventional Agatston scoring procedure. Multi-slice CT coronary angiograms using axial, double maximum intensity projections (MIPs) and multiplanar reconstructions were generated and the

presence of significant coronary disease was classified according to the presence of one or more stenosis ≥50% in the major epicardial vessels.

6.3.h Biomarker assays

Both biomarkers assessed in this study were analysed using commercially available assays.

6.3.h.i BNP assay

BNP was assessed using Bayer (now Siemens) Advia Centaur BNP assay which is an automated two site sandwich immunoassay utilising direct chemiluminescent technology. The assay uses two monoclonal antibodies supplied by Shionogi & Co. The first reagent is an acridinium ester labelled monoclonal mouse anti-human BNP $F(ab')_2$ fragment specific to the ring structure of BNP and the second a biotinylated monoclonal mouse anti-human antibody specific to the C-terminal of BNP and is coupled to streptavidin magnetic particles.

The minimum detectable concentration is 2pg/ml, at 20% coefficient of variance functional sensitivity was 2.5pg/ml.[285, 286]

6.3.h.ii High Sensitivity cTnI assay (hsTnI)

Cardiac troponin I levels were measured using the highly sensitive Bayer (now Siemens) chemiluminescent Advia Centaur TnIUltra method. This method uses 2 monoclonal capture antibodies and a tracer polyclonal goat antibody labelled with acridinium ester. Manufacturers data gives lower limit of detection of 0.006 µg/L and the 99th percentile reference value of 0.040 µg/L. Assay total imprecision was reported by Siemens to be 10% at 0.03 µg/L.[287] Similar values were obtained by independent analysis.[288]

6.3.i Statistical methods

Anonymised data were extracted from Excel into SPSS v 17 and analyses were performed by myself.

Data are presented as mean (±standard deviation), however the data pertaining to measures of the biomarkers hs-TnI and BNP were found to be heavily skewed and not normally distributed and could not be normalised through transformation and thus are presented as median (interquartile range).

For comparison of normally distributed data the independent t test was used.

For comparing the change in hs-TnI and BNP pre and post exercise the Wilcoxon signed ranks t-test was used. To compare the levels of BNP and hs-TnI in various groups the Mann-Whitney U test was applied. Troponin levels below the lower limit of detection of the assay were transformed to a value of 0.001 μg/L. Some continuous variables were transformed into categorical data such as calcium score 0 or greater than 0, hs-TnI ≤0.006 μg/L or >0.006 μg/L and data were then compared using the Chi squared test.

6.4 Results

6.4.a Cohort characteristics

I recruited 229 patients into the study, 126 patients successfully underwent CT scans, of these 93 had both calcium scores and CTCA. I defined two groups based on the presence of significant coronary artery disease as determined by CTCA.

Table 24 Demographic and clinical characteristics of cohort (n=229), characteristics represented as n (%).

Age	53 (11)		
Male	170 (74%)		
Racial group	White 67 (29%)	Asian 134 (59%)	Black 28 (12%)

DM	69 (30%)
Hypertension	102 (45%)
Current Smoker	50 (22%)
CCF	1 (0.4%)

There was a majority of South Asian patients consistent with the local population distribution within the catchment area of Newham University Hospital. This no doubt contributed to the high prevalence of diabetes within the cohort, although the prevalence of other risk factors was more consistent with the RACPC populations reported elsewhere.

First I will explore the differences between patients with and without CAD as determined by CTCA paying particular interest to the biomarkers hs-TnI and BNP. I will then explore the response of BNP and hs-TnI to exercise in the whole cohort and subgroups.

6.4.b Anatomic Coronary Artery Disease by CTCA

Table 25 summarises the characteristics of those patients with and without CAD as determined by CTCA. Of the 93 patients for whom calcium score and CTCA were available; 13 had significant coronary artery disease evidenced by one or more luminal stenoses of ≥50% as determined by CTCA.

Patients with CAD were older and had a significantly higher pre-test probability of disease based on Diamond and Forrester criteria. I identified no other significant differences in baseline characteristics between the two groups.

Table 25 Demographic and clinical characteristics in presence or absence of CAD on CTCA. Represented as n (%) or median (IQR).

	Significant Angiographic CAD (≥50%)		P
	Yes (n=13)	No (n=80)	
Age - median (IQR)	56(10)	51 (9.75)	<0.05
Asian Ethnicity - n(%)	8 (61.5)	45 (56.3)	0.87
Women - n(%)	3 (23.1)	10 (27.5)	0.74
Diabetes- n(%)	5 (38.4)	25 (31.2)	0.82
Current Smoker- n(%)	3 (23.1)	22 (27.5)	0.74
Pre-test Prob- median (IQR)	58 (37.6)	54(26.5)	0.02
Creatinine – median (IQR)	96(26)	94(18)	0.37

6.4.c Biomarkers measured after 30 minutes supine rest: associations with anatomic CAD.

90 patients had data for biomarkers available. The distribution of biomarkers was significantly skewed and attempts to transform the data did not render a normalised distribution and thus non-parametric testing was used to test the significance of differences between the groups.

hs-TnI after 30 minutes supine rest was detectable in 65% of all patients and in 37% of patients with both a negative exercise test and no anatomic CAD. Nevertheless hs-TnI tended to be higher in patients with coronary artery disease (median 0.120µg/L IQR 0.10) than without (median 0.007µg/L IQR 0.11) but the difference was not significant.

To examine the difference between patients with troponin values at the extreme lower end of detection and all others I stratified baseline hs-TnI below the lower limit of detection for the hs-TnI assay (0.006 µg/L) as negative creating two groups; those with positive hs-TnI and those with negative hs-TnI. Comparing these groups there was no significant difference in proportions with evidence of anatomic CAD by CTCA (Chi squared p=0.160)

Table 26 Biomarkers at rest: associations with anatomic CAD, coronary calcium score and positive exercise test (ETT).

	CAD		p	Calcium Score (Agatston Units)		p	ETT		p
	Yes	**No**		**0**	**>0**		**Pos**	**neg**	
hs-TnI (µg/L) median(IQR)	0.120(0.10)	0.007(0.11)	0.07	0.007(0.01)	0.009(0.014)	0.07	0.010(0.005)	0.007(0.13)	
Trop +ve (n)	11	50	0.16	39	41	0.33	24	107	0.21
Trop –ve (n)	2	27	0.16	20	14	0.33	7	55	0.21
BNP (pg/ml) Median(IQR)	18.51(25)	9.2(13)	0.02	9.26(13)	12.87(17)	0.08	13.43	9.26	

BNP measured after 30 minutes supine rest was significantly higher in patients with significant coronary disease as determined by CTCA than those without (18.08pg/ml(IQR 22) vs 9.14pg/ml (IQR 12.62), p=0.024)

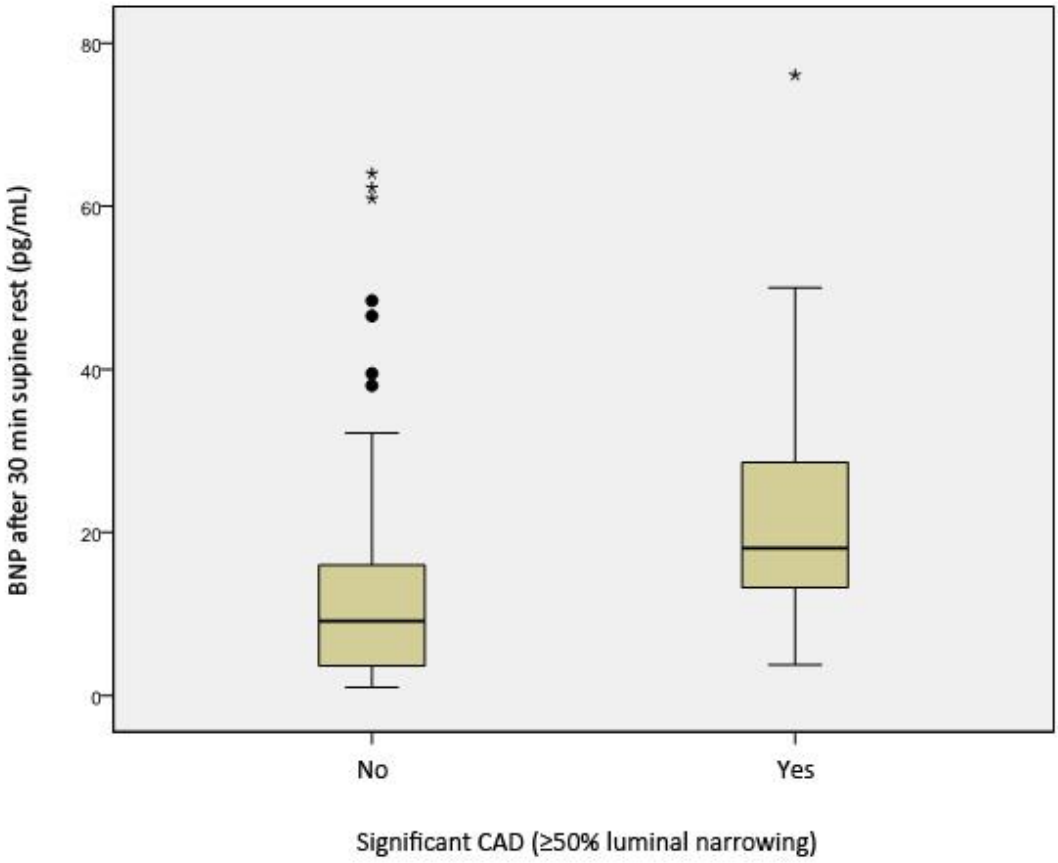


Figure 20 Boxplot of BNP levels at rest in presence or absence of significant CAD by CTCA.

6.4.d Biomarkers after 30 minutes supine rest: associations with coronary calcification

The calcium score was considerably higher in patients with significant CAD by CTCA, but there was no significant difference in hs-TnI or BNP concentrations between patients with and without coronary calcification, as defined by a calcium score of zero (Table 26). Moreover I found no correlation between ca score or BNP (r=0.14 p=0.14) and only a weak correlation between troponin I (r=0.26 p=0.05) and calcium score.

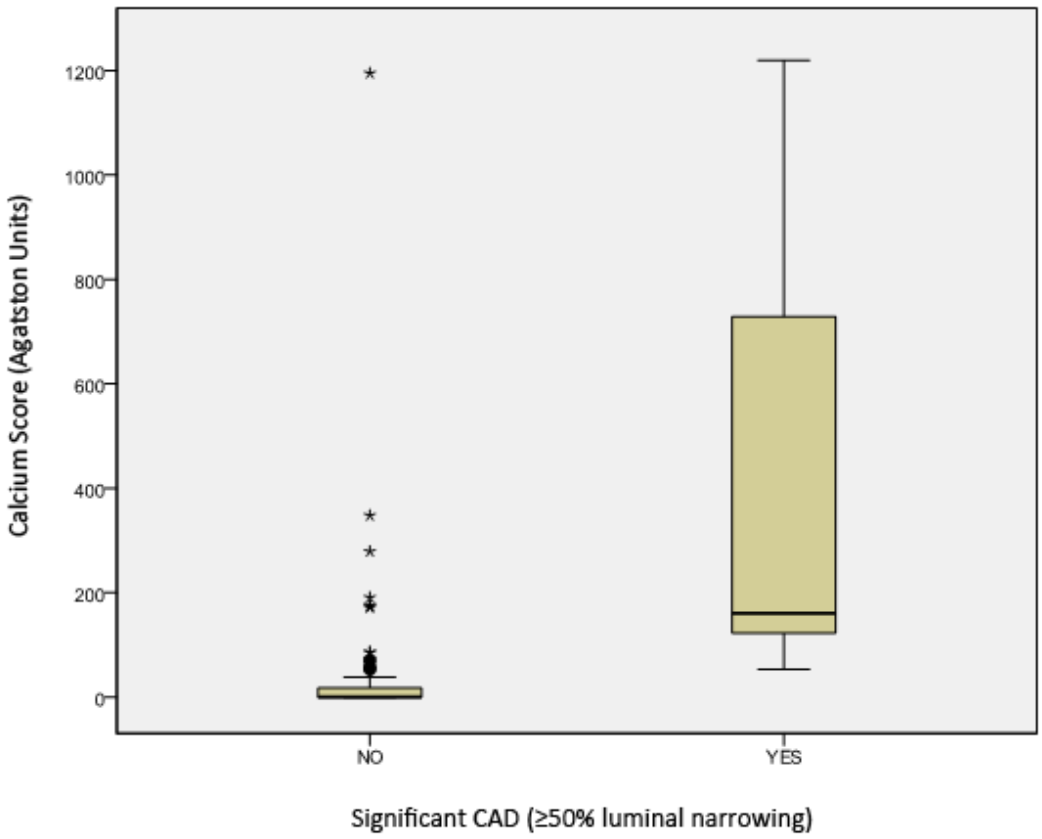


Figure 21 Boxplot of calcium scores in patients with and without significant CAD by CTCA

6.4.e Exertional ischaemia by exercise ECG

Table 27 summarises the characteristics of those patients with and without an abnormal exercise ECG. Of the 113 patients, those with a positive test had a higher pre-test probability of CAD compared with those with negative or inconclusive tests.

Table 27 Demographics, baseline biomarkers and ischaemia by ETT. Displayed as n(%) mean ±SD and median(IQR)

		ETT Ischaemia		p
	Inconclusive	**Negative**	**Positive**	
Age median (IQR)	54 (12)	51(12)	55(15)	0.17
Asian Ethnicity	11 (55.0%)	41 (60.3%)	13 (52.0%)	0.148
Women	8 (40.0%)	15 (22.1%)	5 (20.0%)	0.199
Diabetes	8 (40.0%)	20 (29.4%)	9 (36.0%)	0.161
Current Smoker	4 (20.0%)	20 (29.4%)	2 (8.0%)	0.51
Pre-test Probability	58.9±19.7	47.7±18.8	69.2±23.6	<0.0001
Creatinine	90(22)	90(18)	92(28)	0.63

6.4.f Biomarkers after 30 minutes supine rest: associations with an abnormal exercise ECG.

Table 26 shows there was no significant difference between baseline hs-TnI levels in patients with positive and negative exercise ECGs, and stratification into hs-TnI positive and hs-TnI negative, defined by a hs-TnI ≤0.006> µg/L, showed no significant difference in proportions with and without a positive exercise ECG (p=0.214). However BNP was significantly higher in patients with a positive exercise ECG compared with patients with a negative exercise ECG (13.43pg/ml (IQR 31) vs 9.26pg/ml (IQR 14), p=0.008).

6.4.g Biomarker responses to exercise

Table 28 shows changes in troponin I and BNP levels measured before and 15 minutes after exercise stress testing.

Table 28 Change in biomarker levels with exercise in 90 subjects.

	Pre ETT	Post ETT	p
hs-TnI (µg/L) median (IQR) n=90	0.008 (0.011)	0.008 (0.012)	0.354
BNP (pg/ml) median (IQR) n=90	10.6 (16)	12.5 (19.8)	<0.0001

BNP concentrations increased significantly but exercise had no significant effect on hs-TnI. The increase in BNP concentration tended to be greater in patients with anatomic CAD and in patients with a positive exercise ECG (Table 29) but the differences were not significant. Changes in hs-TnI were always small and unaffected by the presence of anatomic CAD or a positive exercise ECG.

Table 29 Comparison of degree of biomarker change with CAD or ischaemia

	CAD	No CAD	p	ETT positive	ETT negative	p
Δhs-TnI (µg/L) Median (IQR) n=90	0.001(0.01)	0.00(0.01)	0.89	0.002(0.01)	0.00(0.01)	0.24
ΔBNP (pg/ml) Median (IQR) n=90	2.73(5.69)	1.27(3.29)	0.16	2.48(4.77)	1.24(3.16)	0.49

6.5 Discussion

In this chapter I explored the characteristics of a cohort of patients attending a RACPC in north east London and examined the differences in biomarkers at baseline and following exercise, comparing subgroups with and without evidence of ischaemia and anatomic coronary artery disease. I found that in patients with suspected angina, CTCA provides a useful endpoint for assessing the diagnostic value of circulating biomarkers. BNP levels were higher among patients shown to have coronary artery disease although the differences were small and unlikely of diagnostic value. cTnI levels assessed with a high sensitivity assay showed no difference between those with and without coronary artery disease.

Although numbers recruited for this research were small, the findings strongly suggest that hs-TnI has no diagnostic value in patients with undifferentiated chest pain attending chest pain clinics. Thus neither resting serum concentrations nor concentrations measured after exercise distinguished between patients with and without anatomic CAD by CTCA. The apparent conflict with studies in healthy cohorts that have reported troponin elevations after exercise can be resolved by noting that exercise in those studies was considerably more strenuous and prolonged and the

elevation of troponin occurred considerably later than the 15 minute window in my study. Of some interest was the finding that a significant proportion of the cohort had detectable elevations of hs-TnI often with no evidence of CAD or ischaemia on exercise stress testing. The data provide no indication of a mechanism, although it is consistent with the theory of cytosolic leak outlined in chapter 1.

BNP looked potentially more useful as a diagnostic marker than hs-TnI in this group of patients. It was not only higher in patients with anatomic CAD but also increased significantly on exercise, the increase tending to be greater in patients with anatomic coronary disease and patients with exertional ischaemia during stress testing. However, changes were generally quite small and whether BNP can provide any incremental diagnostic value over and above that provided by clinical factors needs testing in larger cohorts. It had been my intention to measure both the TNI and BNP levels again at 24 hours post exercise but very few patients returned for blood sampling. It remains unknown, therefore, whether late post-exercise BNP or hs-TnI measurement might improve diagnostic value, although the poor re-attendance rate in my study suggests that clinical value of late testing would be limited.

6.5.a Comparison with other studies

In chapter 1 I looked at the evidence for troponin and BNP elevation in patients with both stable and unstable coronary disease.

There are several prior studies demonstrating an association between BNP, ischaemia and prognosis, however none of these studies use CTCA as a means to assess the presence of CAD. The present study provides further evidence for the association between raised BNP levels and CAD.

Two other studies have used assays of similar sensitivity to that in the current study to investigate the role of troponin elevation, however they assessed cTnT and not hs-TnI, and no similar study has been published assessing hs-TnI in this circumstance.

In a substudy of the PEACE trial, Omland[289] demonstrated detectable levels of troponin T in 97.7% of patients in a cohort of 3679 patients with stable coronary disease with levels above the 99th percentile value of healthy subjects in 11.1%. Even low levels of

troponin showed correlation with cardiovascular death and heart failure. Myocardial infarction was only found to be weakly correlated in an unadjusted model, and this became statistically insignificant after adjustment for other factors. This is a significantly higher proportion of patients found to have troponin elevation than I found in the present study when examining hs-TnI, although the levels are not directly comparable, but it also provides evidence of the prognostic value of cTnT in the stable setting.

Ndrepepa[290] demonstrated that small baseline troponin T elevations, previously undetectable by the earlier generation of assays, predicted mortality and cardiovascular mortality but not nonfatal myocardial infarction in 808 patients with stable angina even though nearly all patients subsequently underwent revascularisiation with either percutaneous coronary intervention or coronary artery bypass grafting. This cohort had a large percentage of patients with previous CABG or myocardial infarction and although the referral route is not clearly described, it appears that this is a selected group of patients, unlike the cohort assessed in the current study.

The lack of a significant difference between the groups for hs-TnI levels may indicate an important difference in the underlying mechanism between cTnI and cTnT release in this setting and has implications for the further development of this concept. cTnT and cTnI have different release kinetics and different quantities in the free cytosolic pool and the two biomarkers need to be considered separately.

6.5.b Limitations

The main limitations here were the small numbers in the study and the lack of follow up data due in part to poor recruitment and the distance between the assessment sites with reluctance of patients to re-attend for CTCA. A further limitation was the lack of assessment of LV function to help further define the significance of the BNP levels and whether this was confounded by visually measurable differences in LV function. The short time period from exercise to evaluation of post exercise hs-TnI is likely to have reduced the ability to assess the elevation of hs-TnI as the release

kinetics suggest that a later sample might be more informative. This had initially been planned, but the unwillingness of the majority of study participants to return for a repeat test prevented this.

6.6 Chapter summary

In this chapter I demonstrated the usefulness of CTCA as an endpoint when assessing novel diagnostic biomarkers for patients with suspected CAD. The data as presented above show that a significant number of patients presenting with stable chest pain have elevated levels of cardiac troponin I when measured with a highly sensitive assay although no differences were observed between patients with and without anatomic coronary artery disease. Baseline BNP levels, however, were higher in patients with coronary artery disease or myocardial ischaemia and showed a small rise after Bruce protocol testing. However, the differences were not marked and its diagnostic value for coronary artery disease in patients with suspected angina is unlikely to be clinically helpful.

7. SUMMARY

In this work the application of CT technology to the assessment of coronary artery disease has been explored. CT technology has been described and a detailed assessment made of the key limiting factors and the advances that have been made to overcome them allowing CTCA to evolve into a useful clinical tool.

In Chapter 3 an in depth examination of the continuing need to maintain a slow and regular heart beat at time of scan was outlined. Existing studies demonstrating the benefit of lower heart rates were outlined and my own data confirming the association between lower heart rate and image quality was presented. The potential candidates for rate lowering pharmacotherapy where explored and the rationale for my regime explained with the relatively short onset time of oral metoprolol. Other existing strategies were documented and my protocol for heart rate lowering in CTCA was presented with my evidence demonstrating a mean reduction in heart rate in patients following this regime of 17bpm. Although no statistical significance could be demonstrated in this relatively small group, there was a suggestion that the administration of further intravenous metoprolol to non responders of oral therapy made little difference, presenting the need for this to be further explored and alternatives assessed. Only 4 patients received verapamil with universally disappointing results and, although no claims can be made on the basis of these patients, it would be wise to consider alternative strategies at the same time as further assessing verapamil efficacy. One of the potential drugs that could be used in this way is ivabradine, that slows the heart rate only in sinus rhythm through action on the If channel.

Prior to 64 slice CTCA technology it has been shown that CTCA was not sufficiently accurate for routine clinical use and was not able to assess for in stent restenosis. The technical improvements in coverage, temporal and spatial resolution that came with development of the 64 slice CT scanners marked a significant milestone in CTCA technology heralding in more widespread clinical application of CTCA. CTCA was

shown to have good accuracy for assessing native coronary arteries with an excellent negative predictive value. Multi centre trials demonstrated consistently good results for the negative predictive value of the technology but low positive predictive values, which were somewhat less than from the original single centre studies.

Chapter 4 explored the accuracy of CTCA in a cohort of patients all with previously treated coronary artery disease. Similar levels of accuracy were found to those in multi centre trials of CTCA using 64 slice technology, but somewhat lower than those in early adopter centres, who largely investigated lower risk groups. As has been the case through many trials of CTCA I demonstrated a very good negative predictive value, even in this higher risk group of 98.8%, with a considerably lower positive predictive value. This demonstrates that even in patients with previously treated coronary artery disease unstented vessels can be shown to be free of significant stenoses with considerable confidence. However, the positive predictive value of CTCA64 for coronary artery disease is too low for diagnostic purposes and its clinical use is best reserved for rule out in patients with a low probability of disease.

In Chapter 5 I described the difficulties of coronary artery stent assessment both with conventional invasive coronary angiography (CAX) and CTCA. The limits of CTCA spatial resolution and the susceptibility to blooming artefact renders stent assessment harder than native vessel assessment. Much of the previous studies of the accuracy had compared these two flawed standards with each other. In the study presented I compared CTCA and CAX with intravascular ultrasound (IVUS) and found that both had difficulty correctly identifying significant in stent restenosis compared with IVUS as a gold standard. My results in CTCA were somewhat worse than those in other studies outlined, however my cohort included a significant number of large strut stents of older designs and this may have contributed to this difference. CTCA as performed in this study cannot be advocated for the assessment of stented arteries. Developments in the field of CT technology have been fast and whilst some reduction in motion and stitch artefact has been reduced with the implementation of larger detectors with increased coverage, there has not been a significant increase in the spatial resolution of the technology. The implementation of iterative reconstruction technology reduces

noise in the images and may provide an advantage to the assessment of stents which when combined with the other marginal improvements may lead to an increased accuracy in this setting.

In Chapter 6 I investigated the utility of CTCA as an endpoint for evaluation of novel biomarkers in the setting of rapid access chest pain clinics. The cohort investigated had a significant number of patients with South Asian ethnic origin from a poor area of London. I measured baseline and post exercise hs-TnI and BNP levels in a cohort of patients with suspected angina, comparing subgroups with and without CTCA evidence of coronary disease. I found no difference in baseline hs-TnI levels between the groups but BNP showed significant elevation in patients with coronary disease on CTCA. However, the difference was small and clinical utility is doubtful.
Response of biomarkers to exercise was also investigated and while hs-TnI was unchanged, a significant rise in BNP was identified, and this was more marked in patients with than without CAD. Whether BNP will find a role in diagnosis of CAD in patients with suspected angina will need further studies in larger groups in order to determine its incremental value over and above clinical factors and simple non-invasive tests.

7.1 Limitations

In assessing the heart rate reduction regime the absence of a control group reduces the value of the study. A larger study with a randomised placebo group would be preferable. Reluctance to perform a technique involving administration of intravenous contrast agent and the use of ionising radiation made the concept of potentially performing non-diagnostic studies on patients unacceptable within our institution. Whilst the evidence for the efficacy of the rate lowering algorithm had not been proven it had become accepted practice and similar procedures had been adopted elsewhere, supported by the evidence of efficacy of the drugs out of the context of CTCA. An observation of change to heart rate and a measure of the proportion of

patients reaching target heart rate at scan time was felt to be the most useful approach in this context.

When assessing CTCA in coronary arteries and stents, evaluating the inter observer variability would have been useful to improve the validity and applicability of the studies. It would have been useful to increase the number of patients evaluated through IVUS to provide narrower confidence intervals and a more accurate result, however I was limited by resources and the number of patients in whom IVUS could be passed beyond severe lesions.

In assessing CTCA and biomarkers in the RACPC it would have been ideal to obtain follow up data for mortality, MACE and revascularisation in a larger cohort which was not possible within my resources. This would have provided further insight into the utility of CTCA for predicting outcome however is not likely to have altered the findings related to baseline biomarkers in relation to the presence of CAD. With a larger cohort it may also have been possible to start to examine the role of non stenotic coronary plaque on cardiovascular events.

7.2 Future Research

Further evaluation of rate reducing regimes is likely to remain useful in the coming years as the CT temporal resolution increases have generally been marginal with the exception of the development of dual source scanners which are not widespread. Research should be undertaken in a multi centre setting evaluating the efficacy of a rate control regime and other potential drugs such as ivabradine warrant further assessment.

As CT technology has developed at great speed in recent years, scanners with larger detector coverage and higher rotation speeds have become increasingly available with improved reconstruction techniques leading to a reduction in image artefact. Thus far there has been only marginal improvement in spatial resolution compared to the scanner used in my research and this is a key factor in improving the ability of CT technology to accurately assess coronary artery disease in high risk groups and is

particularly important for the assessment of stent restenosis. Research to assess the cumulative effect of the continual small advances made is useful and is ongoing but a key milestone is likely to be seen when a significant change in spatial resolution can be achieved.

BNP showed some potential within the stable CAD patients assessed in chapter 6 and this warrants investigation with follow up in a larger group of patients to determine the incremental value of BNP in addition to existing risk scoring algorithms.

CTCA has the potential to become a modality that can non invasively assess non stenotic coronary plaque, this presents the possibility to identify coronary artery disease at a much earlier stage in development. This would require very large numbers of patients to be studied over a long period due to the small number of events expected and would only be useful if an additional intervention could be made that would alter the prognosis in those identified at risk of cardiovascular events.

7.3 Conclusion

In this thesis I have provided an analysis of CTCA technology with particular emphasis on 64 slice scanners. I have presented a heart rate lowering strategy with evidence of efficacy and provided further evidence of the link between heart rate and image quality. CTCA64 has been demonstrated to have good negative predictive value in the non-diseased arterial segments of patients with known CAD but its positive predictive accuracy for significant luminal obstruction is low limiting its clinical application. I have also shown that CTCA64 cannot reliably identify in-stent restenosis, although its performance is little worse than invasive angiography when compared with an IVUS gold standard. There is however huge promise in the technology with continual developments and rapid progress which are likely to further enhance its application for coronary imaging. Meanwhile CTCA has important research potential for providing an anatomic endpoint in studies of novel biomarkers. In this thesis, I have shown that, despite the important clinical application of cTnI and BNP for diagnosis of myocardial

infarction and heart failure, these biomarkers are unlikely to have a useful role for diagnosing CAD in patients with suspected angina attending chest pain clinics.

8. REFERENCES

1. Libby, P., P.M. Ridker, and G.K. Hansson, *Progress and challenges in translating the biology of atherosclerosis.* Nature, 2011. **473**(7347): p. 317-25.
2. Weber, C. and H. Noels, *Atherosclerosis: current pathogenesis and therapeutic options.* Nat Med, 2011. **17**(11): p. 1410-22.
3. Falk, E., *Pathogenesis of atherosclerosis.* J Am Coll Cardiol, 2006. **47**(8 Suppl): p. C7-12.
4. Tabas, I., K.J. Williams, and J. Boren, *Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications.* Circulation, 2007. **116**(16): p. 1832-44.
5. Davies, M.J., et al., *Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content.* Br Heart J, 1993. **69**(5): p. 377-81.
6. Virmani, R., et al., *Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions.* Arterioscler Thromb Vasc Biol, 2000. **20**(5): p. 1262-75.
7. Naghavi, M., et al., *From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I.* Circulation, 2003. **108**(14): p. 1664-72.
8. Biasucci, L.M., M. Leo, and G.L. De Maria, *Local and systemic mechanisms of plaque rupture.* Angiology, 2008. **59**(2 Suppl): p. 73S-6S.
9. Libby, P., *Molecular and cellular mechanisms of the thrombotic complications of atherosclerosis.* J Lipid Res, 2009. **50 Suppl**: p. S352-7.
10. Glagov, S., et al., *Compensatory enlargement of human atherosclerotic coronary arteries.* N Engl J Med, 1987. **316**(22): p. 1371-5.
11. Burke, A.P., et al., *Pathophysiology of calcium deposition in coronary arteries.* Herz, 2001. **26**(4): p. 239-44.
12. Doherty, T.M. and R.C. Detrano, *Coronary arterial calcification as an active process: a new perspective on an old problem.* Calcif Tissue Int, 1994. **54**(3): p. 224-30.
13. Stary, H.C., *The sequence of cell and matrix changes in atherosclerotic lesions of coronary arteries in the first forty years of life.* Eur Heart J, 1990. **11 Suppl E**: p. 3-19.
14. Burton, D.G., H. Matsubara, and K. Ikeda, *Pathophysiology of vascular calcification: Pivotal role of cellular senescence in vascular smooth muscle cells.* Exp Gerontol, 2010. **45**(11): p. 819-24.
15. Ehara, S., et al., *Coronary artery calcification revisited.* J Atheroscler Thromb, 2006. **13**(1): p. 31-7.
16. Mazzini, M.J. and P.C. Schulze, *Proatherogenic pathways leading to vascular calcification.* Eur J Radiol, 2006. **57**(3): p. 384-9.
17. Agatston, A.S., et al., *Quantification of coronary artery calcium using ultrafast computed tomography.* J Am Coll Cardiol, 1990. **15**(4): p. 827-32.
18. Rumberger, J.A., et al., *Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study.* Circulation, 1995. **92**(8): p. 2157-62.

19. Sangiorgi, G., et al., *Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology.* J Am Coll Cardiol, 1998. **31**(1): p. 126-33.
20. World Health organisation, *WHO factsheet N0317 updated Sept 2009*, 2009.
21. Allender, S., Scarborough Peter, Peto Viv, Rayner Mike, Leal Jose, Luengo-ernandez Ramon , Gray Alastair, *Data from WHO and Eurostat presented in 'European cardiovascular disease statistics' 2008 edition.*, E.h. network, Editor.
22. British Heart Foundation, *www.heartstats.org/datapage.asp?id=1584*. 2009.
23. Davies, M., et al., *Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study.* Lancet, 2001. **358**(9280): p. 439-44.
24. Fox, K.F., et al., *Coronary artery disease as the cause of incident heart failure in the population.* Eur Heart J, 2001. **22**(3): p. 228-36.
25. Murdoch, D.R., et al., *Importance of heart failure as a cause of death. Changing contribution to overall mortality and coronary heart disease mortality in Scotland 1979-1992.* Eur Heart J, 1998. **19**(12): p. 1829-35.
26. Kagan, A., et al., *The Framingham study: a prospective study of coronary heart disease.* Fed Proc, 1962. **21(4)Pt 2**: p. 52-7.
27. Bhargava, B., et al., *New approaches to preventing restenosis.* BMJ, 2003. **327**(7409): p. 274-9.
28. Di Mario, C., et al., *Quantitative assessment with intracoronary ultrasound of the mechanisms of restenosis after percutaneous transluminal coronary angioplasty and directional coronary atherectomy.* Am J Cardiol, 1995. **75**(12): p. 772-7.
29. Mintz, G.S., et al., *Intravascular Ultrasound Assessment of the Mechanisms and Predictors of Restenosis Following Coronary Angioplasty.* J Invasive Cardiol, 1996. **8**(1): p. 1-14.
30. Hoffmann, R., et al., *Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study.* Circulation, 1996. **94**(6): p. 1247-54.
31. Farb, A., et al., *Pathology of acute and chronic coronary stenting in humans.* Circulation, 1999. **99**(1): p. 44-52.
32. Indolfi, C., et al., *Molecular mechanisms of in-stent restenosis and approach to therapy with eluting stents.* Trends Cardiovasc Med, 2003. **13**(4): p. 142-8.
33. Scanlon, P.J., et al., *ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions.* Circulation, 1999. **99**(17): p. 2345-57.
34. Bashore, T.M., et al., *American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on cardiac catheterization laboratory standards. A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents.* J Am Coll Cardiol, 2001. **37**(8): p. 2170-214.

35. Roberts, W.C. and A.A. Jones, *Quantitation of coronary arterial narrowing at necropsy in sudden coronary death: analysis of 31 patients and comparison with 25 control subjects.* Am J Cardiol, 1979. **44**(1): p. 39-45.
36. Isner, J.M., et al., *Accuracy of angiographic determination of left main coronary arterial narrowing. Angiographic--histologic correlative analysis in 28 patients.* Circulation, 1981. **63**(5): p. 1056-64.
37. White, C.W., et al., *Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis?* N Engl J Med, 1984. **310**(13): p. 819-24.
38. Arnett, E.N., et al., *Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings.* Ann Intern Med, 1979. **91**(3): p. 350-6.
39. Herrington, D.M., et al., *Variability in measures of coronary lumen dimensions using quantitative coronary angiography.* J Am Coll Cardiol, 1993. **22**(4): p. 1068-74.
40. Zir, L.M., et al., *Interobserver variability in coronary angiography.* Circulation, 1976. **53**(4): p. 627-32.
41. De Scheerder, I., et al., *Intravascular ultrasound versus angiography for measurement of luminal diameters in normal and diseased coronary arteries.* Am Heart J, 1994. **127**(2): p. 243-51.
42. Fujimoto, J.G., et al., *High resolution in vivo intra-arterial imaging with optical coherence tomography.* Heart, 1999. **82**(2): p. 128-33.
43. Galbraith, J.E., M.L. Murphy, and N. de Soyza, *Coronary angiogram interpretation. Interobserver variability.* JAMA, 1978. **240**(19): p. 2053-6.
44. Hausmann, D., et al., *The safety of intracoronary ultrasound. A multicenter survey of 2207 examinations.* Circulation, 1995. **91**(3): p. 623-30.
45. Batkoff, B.W. and D.T. Linker, *Safety of intracoronary ultrasound: data from a Multicenter European Registry.* Cathet Cardiovasc Diagn, 1996. **38**(3): p. 238-41.
46. Gorge G, P.R., Pinto F, Distante A, Visser C, Fraser A, Erbel R, *Intravascular Ultrasound: Safety and Inications for Use in 7035 Consecutive Patients Studied in 32 centres in Europe and Israel.* Journal of the American College of Cardiology, 1996. **27**(February): p. 155A-155A.
47. Nicholls, S.J., et al., *Effect of two intensive statin regimens on progression of coronary disease.* N Engl J Med, 2011. **365**(22): p. 2078-87.
48. Nakamura, S., et al., *Intracoronary ultrasound observations during stent implantation.* Circulation, 1994. **89**(5): p. 2026-34.
49. Ito, K., et al., *Impact of coronary artery remodeling on misinterpretation of angiographic disease eccentricity: evidence from intravascular ultrasound.* Int J Cardiol, 1999. **70**(3): p. 275-82.
50. Rontgen, W.C. *Nobel Lecture*. 1901. Stockholm, Sweden.
51. Hounsfield, G.N., *Nobel lecture, 8 December 1979. Computed medical imaging.* J Radiol, 1980. **61**(6-7): p. 459-68.
52. Flohr, T.G., et al., *First performance evaluation of a dual-source CT (DSCT) system.* European radiology, 2006. **16**(2): p. 256-68.
53. Supplied by Siemens - unpublished internal document.

54. Lee, K.W. and J. Panting, *Current status of non-invasive coronary angiography for the diagnosis of coronary artery stenosis.* Review Literature And Arts Of The Americas, 2006. **13**(2): p. 49-56.
55. ImPACT, Impact, St George's Hospital: London.
56. Becker, C.R., et al., *Detection and quantification of coronary artery calcification with electron-beam and conventional CT.* Eur Radiol, 1999. **9**(4): p. 620-4.
57. Greuter, M.J.W., et al., *A model for temporal resolution of multidetector computed tomography of coronary arteries in relation to rotation time, heart rate and reconstruction algorithm.* European radiology, 2007. **17**(3): p. 784-812.
58. Herzog, C., et al., *Does two-segment image reconstruction at 64-section CT coronary angiography improve image quality and diagnostic accuracy?* Radiology, 2007. **244**(1): p. 121-9.
59. Dewey, M., H. Hoffmann, and B. Hamm, *Multislice CT coronary angiography: effect of sublingual nitroglycerine on the diameter of coronary arteries.* Rofo, 2006. **178**(6): p. 600-4.
60. Onuma, Y., et al., *Noncardiac findings in cardiac imaging with multidetector computed tomography.* Journal of the American College of Cardiology, 2006. **48**(2): p. 402-6.
61. Thomas, G.S., C.L. Martinez, and D.L. Rice, *Sequential myocardial perfusion imaging and cardiac CT: what to do with incidental CT findings?* Am Heart Hosp J, 2006. **4**(1): p. 71-3.
62. Schragin, J.G., et al., *Non-cardiac findings on coronary electron beam computed tomography scanning.* Journal of thoracic imaging, 2004. **19**(2): p. 82-6.
63. Coles, D.R., et al., *Comparison of radiation doses from multislice computed tomography coronary angiography and conventional diagnostic angiography.* Journal of the American College of Cardiology, 2006. **47**(9): p. 1840-5.
64. National Research Council (U.S.). Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation., *Health risks from exposure to low levels of ionizing radiation : BEIR VII Phase 2*2006, Washington, D.C.: National Academies Press. xvi, 406 p.
65. Huda, W., K.M. Ogden, and M.R. Khorasani, *Converting dose-length product to effective dose at CT.* Radiology, 2008. **248**(3): p. 995-1003.
66. Hausleiter, J.r., et al., *Radiation dose estimates from cardiac multislice computed tomography in daily practice: impact of different scanning protocols on effective dose estimates.* Circulation, 2006. **113**(10): p. 1305-10.
67. Deetjen, A., et al., *Use of automatic exposure control in multislice computed tomography of the coronaries: comparison of 16-slice and 64-slice scanner data with conventional coronary angiography.* Heart, 2007. **93**(9): p. 1040-3.
68. Zanzonico, P., L.N. Rothenberg, and H.W. Strauss, *Radiation exposure of computed tomography and direct intracoronary angiography: risk has its reward.* Journal of the American College of Cardiology, 2006. **47**(9): p. 1846-9.
69. Vijayalakshmi, K., et al., *Cardiac catheterisation: radiation doses and lifetime risk of malignancy.* Heart, 2007. **93**(3): p. 370-1.
70. Hausleiter, J., et al., *Image quality and radiation exposure with prospectively ECG-triggered axial scanning for coronary CT angiography: the multicenter,*

multivendor, randomized PROTECTION-III study. JACC Cardiovasc Imaging, 2012. **5**(5): p. 484-93.
71. Leschka, S., et al., *Diagnostic accuracy of high-pitch dual-source CT for the assessment of coronary stenoses: first experience.* Eur Radiol, 2009. **19**(12): p. 2896-903.
72. Sabarudin, A., Z. Sun, and K.H. Ng, *A systematic review of radiation dose associated with different generations of multidetector CT coronary angiography.* J Med Imaging Radiat Oncol, 2012. **56**(1): p. 5-17.
73. Alkadhi, H., et al., *Aortic stenosis: comparative evaluation of 16-detector row CT and echocardiography.* Radiology, 2006. **240**(1): p. 47-55.
74. Bouvier, E., et al., *Diagnosis of aortic valvular stenosis by multislice cardiac computed tomography.* Eur Heart J, 2006. **27**(24): p. 3033-8.
75. Fraser, A.G., et al., *The future of cardiovascular imaging and non-invasive diagnosis: a joint statement from the European Association of Echocardiography, the Working Groups on Cardiovascular Magnetic Resonance, Computers in Cardiology, and Nuclear Cardiology, of the European.* European heart journal, 2006. **27**(14): p. 1750-3.
76. Gershlick, A.H., et al., *Role of non-invasive imaging in the management of coronary artery disease: an assessment of likely change over the next 10 years. A report from the British Cardiovascular Society Working Group.* Heart, 2007. **93**(4): p. 423-31.
77. Ozgun, M., et al., *Intraindividual comparison of 3D coronary MR angiography and coronary CT angiography.* Acad Radiol, 2007. **14**(8): p. 910-6.
78. Schuijf, J.D., et al., *Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for noninvasive coronary angiography.* Am Heart J, 2006. **151**(2): p. 404-11.
79. Mori, S., et al., *Effective doses in subjects undergoing computed tomography cardiac imaging with the 256-multislice CT scanner.* European journal of radiology, 2008. **65**(3): p. 442-8.
80. Gupta, R., et al., *Ultra-high resolution flat-panel volume CT: fundamental principles, design architecture, and system characterization.* European radiology, 2006. **16**(6): p. 1191-205.
81. Gupta, R., et al., *Flat-panel volume CT: fundamental principles, technology, and applications.* Radiographics, 2008. **28**(7): p. 2009-22.
82. GE Healthcare promotional material.
83. Silva, A.C., et al., *Innovations in CT dose reduction strategy: application of the adaptive statistical iterative reconstruction algorithm.* AJR Am J Roentgenol, 2010. **194**(1): p. 191-9.
84. Gosling, O., et al., *A comparison of radiation doses between state-of-the-art multislice CT coronary angiography with iterative reconstruction, multislice CT coronary angiography with standard filtered back-projection and invasive diagnostic coronary angiography.* Heart, 2010. **96**(12): p. 922-6.
85. Renker, M., et al., *Evaluation of heavily calcified vessels with coronary CT angiography: comparison of iterative and filtered back projection image reconstruction.* Radiology, 2011. **260**(2): p. 390-9.

86. Wang, R., et al., *Image quality and radiation dose of low dose coronary CT angiography in obese patients: Sinogram affirmed iterative reconstruction versus filtered back projection.* Eur J Radiol, 2012.
87. Leipsic, J., B.G. Heilbron, and C. Hague, *Iterative reconstruction for coronary CT angiography: finding its way.* Int J Cardiovasc Imaging, 2012. **28**(3): p. 613-20.
88. Budoff, M.J., et al., *Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients.* J Am Coll Cardiol, 2007. **49**(18): p. 1860-70.
89. Detrano, R., et al., *Coronary calcium as a predictor of coronary events in four racial or ethnic groups.* N Engl J Med, 2008. **358**(13): p. 1336-45.
90. Kwon, S.W., et al., *Coronary artery calcium scoring does not add prognostic value to standard 64-section CT angiography protocol in low-risk patients suspected of having coronary artery disease.* Radiology, 2011. **259**(1): p. 92-9.
91. Nieman, K., *Reliable Noninvasive Coronary Angiography With Fast Submillimeter Multislice Spiral Computed Tomography.* Circulation, 2002. **106**(16): p. 2051-2054.
92. Ropers, D., *Detection of Coronary Artery Stenoses With Thin-Slice Multi-Detector Row Spiral Computed Tomography and Multiplanar Reconstruction.* Circulation, 2003. **107**(5): p. 664-666.
93. Dewey, M., et al., *Multisegment and Halfscan Reconstruction of 16-Slice Computed Tomography for Detection of Coronary Artery Stenoses.* Investigative Radiology, 2004. **39**(4): p. 223-229.
94. Martuscelli, E., et al., *Accuracy of thin-slice computed tomography in the detection of coronary stenoses.* European heart journal, 2004. **25**(12): p. 1043-8.
95. Kuettner, A., et al., *Noninvasive detection of coronary lesions using 16-detector multislice spiral computed tomography technology: initial clinical results.* Journal of the American College of Cardiology, 2004. **44**(6): p. 1230-7.
96. Mollet, N.R., et al., *Multislice spiral computed tomography coronary angiography in patients with stable angina pectoris.* Journal of the American College of Cardiology, 2004. **43**(12): p. 2265-70.
97. Kuettner, A., et al., *Diagnostic accuracy of noninvasive coronary imaging using 16-detector slice spiral computed tomography with 188 ms temporal resolution.* Journal of the American College of Cardiology, 2005. **45**(1): p. 123-7.
98. Mollet, N.R., et al., *Improved diagnostic accuracy with 16-row multi-slice computed tomography coronary angiography.* Journal of the American College of Cardiology, 2005. **45**(1): p. 128-32.
99. Achenbach, S., et al., *Detection of coronary artery stenoses using multi-detector CT with 16 x 0.75 collimation and 375 ms rotation.* European heart journal, 2005. **26**(19): p. 1978-86.
100. Hoffmann, M.H.K., et al., *Noninvasive coronary angiography with multislice computed tomography.* JAMA : the journal of the American Medical Association, 2005. **293**(20): p. 2471-8.

101. Schuijf, J.D., et al., *Noninvasive coronary imaging and assessment of left ventricular function using 16-slice computed tomography.* The American journal of cardiology, 2005. **95**(5): p. 571-4.
102. Garcia, M.J., J. Lessick, and M.H.K. Hoffmann, *Accuracy of 16-row multidetector computed tomography for the assessment of coronary artery stenosis.* JAMA : the journal of the American Medical Association, 2006. **296**(4): p. 403-11.
103. Leschka, S., et al., *Accuracy of MSCT coronary angiography with 64-slice technology: first experience.* European heart journal, 2005. **26**(15): p. 1482-7.
104. Leber, A.W., et al., *Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound.* Journal of the American College of Cardiology, 2005. **46**(1): p. 147-54.
105. Raff, G.L., et al., *Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography.* Journal of the American College of Cardiology, 2005. **46**(3): p. 552-7.
106. Mollet, N.R., et al., *High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography.* Circulation, 2005. **112**(15): p. 2318-23.
107. Pugliese, F., et al., *Diagnostic accuracy of non-invasive 64-slice CT coronary angiography in patients with stable angina pectoris.* European radiology, 2006. **16**(3): p. 575-82.
108. Malagutti, P., et al., *Use of 64-slice CT in symptomatic patients after coronary bypass surgery : evaluation of grafts and coronary arteries.* European Heart Journal, 2006.
109. Fine, J.J., et al., *Comparison of accuracy of 64-slice cardiovascular computed tomography with coronary angiography in patients with suspected coronary artery disease.* The American journal of cardiology, 2006. **97**(2): p. 173-4.
110. Ropers, D., et al., *Usefulness of multidetector row spiral computed tomography with 64- x 0.6-mm collimation and 330-ms rotation for the noninvasive detection of significant coronary artery stenoses.* The American journal of cardiology, 2006. **97**(3): p. 343-8.
111. Plass, A., et al., *Coronary artery imaging with 64-slice computed tomography from cardiac surgical perspective.* European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery, 2006. **30**(1): p. 109-16.
112. Ehara, M., et al., *Diagnostic accuracy of 64-slice computed tomography for detecting angiographically significant coronary artery stenosis in an unselected consecutive patient population: comparison with conventional invasive angiography.* Circulation journal : official journal of the Japanese Circulation Society, 2006. **70**(5): p. 564-71.
113. Schuijf, J.D., et al., *Diagnostic accuracy of 64-slice multislice computed tomography in the noninvasive evaluation of significant coronary artery disease.* The American journal of cardiology, 2006. **98**(2): p. 145-8.

114. Olivetti, L., et al., *Multislice CT in emergency room management of patients with chest pain and medium-low probability of acute coronary syndrome.* La Radiologia medica, 2006. **111**(8): p. 1054-63.
115. Hamon, M.l., et al., *Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis.* Journal of the American College of Cardiology, 2006. **48**(9): p. 1896-910.
116. Meijboom, W.B., et al., *Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study.* J Am Coll Cardiol, 2008. **52**(25): p. 2135-44.
117. Budoff, M.J., et al., *Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial.* J Am Coll Cardiol, 2008. **52**(21): p. 1724-32.
118. Arbab-Zadeh, A., et al., *Diagnostic accuracy of computed tomography coronary angiography according to pre-test probability of coronary artery disease and severity of coronary arterial calcification. The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) International Multicenter Study.* J Am Coll Cardiol, 2012. **59**(4): p. 379-87.
119. Guo, S.L., et al., *Diagnostic accuracy of first generation dual-source computed tomography in the assessment of coronary artery disease: a meta-analysis from 24 studies.* Int J Cardiovasc Imaging, 2011. **27**(6): p. 755-71.
120. Chao, S.P., et al., *The diagnostic accuracy of 256-row computed tomographic angiography compared with invasive coronary angiography in patients with suspected coronary artery disease.* Eur Heart J, 2010. **31**(15): p. 1916-23.
121. de Graaf, F.R., et al., *Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography in the non-invasive evaluation of significant coronary artery disease.* Eur Heart J, 2010. **31**(15): p. 1908-15.
122. Schlosser, T., et al., *Noninvasive visualization of coronary artery bypass grafts using 16-detector row computed tomography.* Journal of the American College of Cardiology, 2004. **44**(6): p. 1224-9.
123. Burgstahler, C., et al., *Non-invasive evaluation of coronary artery bypass grafts using 16-row multi-slice computed tomography with 188 ms temporal resolution.* International journal of cardiology, 2006. **106**(2): p. 244-9.
124. Anders, K., et al., *Coronary artery bypass graft (CABG) patency: assessment with high-resolution submillimeter 16-slice multidetector-row computed tomography (MDCT) versus coronary angiography.* European journal of radiology, 2006. **57**(3): p. 336-44.
125. Stauder, N.I., et al., *Coronary artery bypass grafts: assessment of graft patency and native coronary artery lesions using 16-slice MDCT.* European radiology, 2006. **16**(11): p. 2512-20.

126. Pache, G., et al., *Initial experience with 64-slice cardiac CT: non-invasive visualization of coronary artery bypass grafts.* European heart journal, 2006. **27**(8): p. 976-80.
127. Ropers, D., et al., *Diagnostic Accuracy of Noninvasive Coronary Angiography in Patients After Bypass Surgery Using 64-Slice Spiral Computed Tomography With 330-ms Gantry Rotation.* Continuing Medical Education, 2006: p. 2334-2341.
128. Henneman, M.M., et al., *Assessment of global and regional left ventricular function and volumes with 64-slice MSCT: a comparison with 2D echocardiography.* Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology, 2006. **13**(4): p. 480-7.
129. Sugeng, L., et al., *Quantitative assessment of left ventricular size and function: side-by-side comparison of real-time three-dimensional echocardiography and computed tomography with magnetic resonance reference.* Circulation, 2006. **114**(7): p. 654-61.
130. Tops, L.F., et al., *Fusion of electroanatomical activation maps and multislice computed tomography to guide ablation of a focal atrial tachycardia in a fontan patient.* Journal of cardiovascular electrophysiology, 2006. **17**(4): p. 431-4.
131. Datta, J., et al., *Anomalous coronary arteries in adults: depiction at multi-detector row CT angiography.* Radiology, 2005. **235**(3): p. 812-8.
132. Gao, D., et al., *Computed tomography for detecting coronary artery plaques: a meta-analysis.* Atherosclerosis, 2011. **219**(2): p. 603-9.
133. George, R.T., et al., *Multidetector computed tomography myocardial perfusion imaging during adenosine stress.* Journal of the American College of Cardiology, 2006. **48**(1): p. 153-60.
134. Morrow, D.A. and E. Braunwald, *Future of biomarkers in acute coronary syndromes: moving toward a multimarker strategy.* Circulation, 2003. **108**(3): p. 250-2.
135. Hochholzer, W., D.A. Morrow, and R.P. Giugliano, *Novel biomarkers in cardiovascular disease: update 2010.* Am Heart J, 2010. **160**(4): p. 583-94.
136. *Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature.* Circulation, 1979. **59**(3): p. 607-9.
137. Ladenson, J., *A personal history of markers of myocyte injury.* Clinica Chimica Acta, 2007. **381**: p. 3-8.
138. registers., W.g.o.t.e.o.i.h.d., *Report of the fifth working group, Copenhagen* 1971, World Health Organization: Geneva.
139. Thygesen, K., J.S. Alpert, and H.D. White, *Universal definition of myocardial infarction.* Eur Heart J, 2007. **28**(20): p. 2525-38.
140. Katus, H.A., et al., *Diagnostic efficiency of troponin T measurements in acute myocardial infarction.* Circulation, 1991. **83**(3): p. 902-12.
141. Jaffe, A.S., et al., *It's time for a change to a troponin standard.* Circulation, 2000. **102**(11): p. 1216-20.

142. Bleier, J., et al., *Different intracellular compartmentations of cardiac troponins and myosin heavy chains: a causal connection to their different early release after myocardial damage.* Clin Chem, 1998. **44**(9): p. 1912-8.
143. Madsen, L.H., et al., *Time course of degradation of cardiac troponin I in patients with acute ST-elevation myocardial infarction: the ASSENT-2 troponin substudy.* Circ Res, 2006. **99**(10): p. 1141-7.
144. Agewall, S., et al., *Troponin elevation in coronary vs. non-coronary disease.* Eur Heart J, 2011. **32**(4): p. 404-11.
145. Ottani, F., et al., *Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes.* Am Heart J, 2000. **140**(6): p. 917-27.
146. Babuin, L. and A.S. Jaffe, *Troponin: the biomarker of choice for the detection of cardiac injury.* Cmaj, 2005. **173**(10): p. 1191-202.
147. Roongsritong, C., I. Warraich, and C. Bradley, *Common causes of troponin elevations in the absence of acute myocardial infarction: incidence and clinical significance.* Chest, 2004. **125**(5): p. 1877-84.
148. Shave, R., et al., *Exercise-induced cardiac troponin T release: a meta-analysis.* Med Sci Sports Exerc, 2007. **39**(12): p. 2099-106.
149. Katus, H.A., et al., *Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction.* Am J Cardiol, 1991. **67**(16): p. 1360-7.
150. Muller-Bardorff, M., et al., *Release kinetics of cardiac troponin T in survivors of confirmed severe pulmonary embolism.* Clin Chem, 2002. **48**(4): p. 673-5.
151. Wiessner, R., et al., *Impact of kidney function on plasma troponin concentrations after coronary artery bypass grafting.* Nephrol Dial Transplant, 2008. **23**(1): p. 231-8.
152. Diris, J.H., et al., *Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients.* Circulation, 2004. **109**(1): p. 23-5.
153. Mousavi, N., et al., *Relation of biomarkers and cardiac magnetic resonance imaging after marathon running.* Am J Cardiol, 2009. **103**(10): p. 1467-72.
154. Niemela, K.O., et al., *Evidence of impaired left ventricular performance after an uninterrupted competitive 24 hour run.* Circulation, 1984. **70**(3): p. 350-6.
155. Raman, S.V., et al., *Cardiac magnetic resonance with edema imaging identifies myocardium at risk and predicts worse outcome in patients with non-ST-segment elevation acute coronary syndrome.* J Am Coll Cardiol, 2010. **55**(22): p. 2480-8.
156. Locca, D., et al., *New universal definition of myocardial infarction applicable after complex percutaneous coronary interventions?* JACC Cardiovasc Interv, 2010. **3**(9): p. 950-8.
157. Bekkers, S.C., et al., *Microvascular obstruction: underlying pathophysiology and clinical diagnosis.* J Am Coll Cardiol, 2010. **55**(16): p. 1649-60.
158. Remppis, A., et al., *Intracellular compartmentation of troponin T: release kinetics after global ischemia and calcium paradox in the isolated perfused rat heart.* J Mol Cell Cardiol, 1995. **27**(2): p. 793-803.

159. Clarke, M.S., et al., *Contraction-induced cell wounding and release of fibroblast growth factor in heart.* Circ Res, 1995. **76**(6): p. 927-34.
160. McNeil, P.L. and R. Khakee, *Disruptions of muscle fiber plasma membranes. Role in exercise-induced damage.* Am J Pathol, 1992. **140**(5): p. 1097-109.
161. Sadoshima, J. and S. Izumo, *Mechanical stretch rapidly activates multiple signal transduction pathways in cardiac myocytes: potential involvement of an autocrine/paracrine mechanism.* EMBO J, 1993. **12**(4): p. 1681-92.
162. Fischer, T.A., et al., *Cardiac myocyte membrane wounding in the abruptly pressure-overloaded rat heart under high wall stress.* Hypertension, 1997. **30**(5): p. 1041-6.
163. Chocron, S., et al., *Effects of myocardial ischemia on the release of cardiac troponin I in isolated rat hearts.* J Thorac Cardiovasc Surg, 1996. **112**(2): p. 508-13.
164. Suleiman, M.S., et al., *Short periods of regional ischaemia and reperfusion provoke release of troponin I from the human hearts.* Clin Chim Acta, 1999. **284**(1): p. 25-30.
165. Feng, Y.J., et al., *Comparison of cardiac troponin I, creatine kinase-MB, and myoglobin for detection of acute ischemic myocardial injury in a swine model.* Am J Clin Pathol, 1998. **110**(1): p. 70-7.
166. Chen, Y., et al., *Cardiac troponin T alterations in myocardium and serum of rats after stressful, prolonged intense exercise.* J Appl Physiol, 2000. **88**(5): p. 1749-55.
167. Tung, P., et al., *Predictors of neurocardiogenic injury after subarachnoid hemorrhage.* Stroke, 2004. **35**(2): p. 548-51.
168. de Feyter, P.J., et al., *Ischemia-related lesion characteristics in patients with stable or unstable angina. A study with intracoronary angioscopy and ultrasound.* Circulation, 1995. **92**(6): p. 1408-13.
169. Mann, J.M., et al., *Histological patterns of atherosclerotic plaques in unstable angina patients vary according to clinical presentation.* Heart, 1998. **80**(1): p. 19-22.
170. Jang, I.K., et al., *In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography.* Circulation, 2005. **111**(12): p. 1551-5.
171. Mann, J. and M.J. Davies, *Mechanisms of progression in native coronary artery disease: role of healed plaque disruption.* Heart, 1999. **82**(3): p. 265-8.
172. Carlson, R.J., et al., *Effect of myocardial ischemia on cardiac troponin I and T.* Am J Cardiol, 2002. **89**(2): p. 224-6.
173. Thayapran, N., et al., *Is there a release of cardiac troponin during exercise testing?* Circulation 1997. **96(Suppl)**: p. I461.
174. Kokowicz, P., et al., *[Troponin release following exercise test in patients with stable angina pectoris - risk factors and prognostic significance].* Kardiol Pol, 2010. **68**(4): p. 414-9; discussion 420-1.
175. Eggers, K.M., et al., *Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects.* Eur Heart J, 2008. **29**(18): p. 2252-8.

176. Wallace, T.W., et al., *Prevalence and determinants of troponin T elevation in the general population.* Circulation, 2006. **113**(16): p. 1958-65.
177. Venge, P., et al., *Normal plasma levels of cardiac troponin I measured by the high-sensitivity cardiac troponin I access prototype assay and the impact on the diagnosis of myocardial ischemia.* J Am Coll Cardiol, 2009. **54**(13): p. 1165-72.
178. Lisy, O., et al., *Therapeutic actions of a new synthetic vasoactive and natriuretic peptide, dendroaspis natriuretic peptide, in experimental severe congestive heart failure.* Hypertension, 2001. **37**(4): p. 1089-94.
179. Richards, A.M., et al., *Dendroaspis natriuretic peptide: endogenous or dubious?* Lancet, 2002. **359**(9300): p. 5-6.
180. Maeda, K., et al., *Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction.* Am Heart J, 1998. **135**(5 Pt 1): p. 825-32.
181. Yoshimura, M., et al., *Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure.* Circulation, 1993. **87**(2): p. 464-9.
182. Pemberton, C.J., et al., *Deconvolution analysis of cardiac natriuretic peptides during acute volume overload.* Hypertension, 2000. **36**(3): p. 355-9.
183. Holmes, S.J., et al., *Renal, endocrine, and hemodynamic effects of human brain natriuretic peptide in normal man.* J Clin Endocrinol Metab, 1993. **76**(1): p. 91-6.
184. Kroll, M.H., P.J. Twomey, and P. Srisawasdi, *Using the single-compartment ratio model to calculate half-life, NT-proBNP as an example.* Clin Chim Acta, 2007. **380**(1-2): p. 197-202.
185. Mukoyama, M., et al., *Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide.* J Clin Invest, 1991. **87**(4): p. 1402-12.
186. Potter, L.R., S. Abbey-Hosch, and D.M. Dickey, *Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions.* Endocr Rev, 2006. **27**(1): p. 47-72.
187. Tamura, N., et al., *Cardiac fibrosis in mice lacking brain natriuretic peptide.* Proc Natl Acad Sci U S A, 2000. **97**(8): p. 4239-44.
188. Nakanishi, M., et al., *Role of natriuretic peptide receptor guanylyl cyclase-A in myocardial infarction evaluated using genetically engineered mice.* Hypertension, 2005. **46**(2): p. 441-7.
189. Bibbins-Domingo, K., et al., *B-type natriuretic peptide and ischemia in patients with stable coronary disease: data from the Heart and Soul study.* Circulation, 2003. **108**(24): p. 2987-92.
190. Toth, M., et al., *Hypoxia stimulates release of ANP and BNP from perfused rat ventricular myocardium.* Am J Physiol, 1994. **266**(4 Pt 2): p. H1572-80.
191. D'Souza, S.P., et al., *B-type natriuretic peptide limits infarct size in rat isolated hearts via KATP channel opening.* Am J Physiol Heart Circ Physiol, 2003. **284**(5): p. H1592-600.

192. Hama, N., et al., *Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction.* Circulation, 1995. **92**(6): p. 1558-64.
193. Goetze, J.P., et al., *Acute myocardial hypoxia increases BNP gene expression.* FASEB J, 2004. **18**(15): p. 1928-30.
194. Goetze, J.P., et al., *Increased cardiac BNP expression associated with myocardial ischemia.* FASEB J, 2003. **17**(9): p. 1105-7.
195. Tateishi, J., et al., *Transient increase in plasma brain (B-type) natriuretic peptide after percutaneous transluminal coronary angioplasty.* Clin Cardiol, 2000. **23**(10): p. 776-80.
196. Neumayr, G., et al., *Effect of competitive marathon cycling on plasma N-terminal pro-brain natriuretic peptide and cardiac troponin T in healthy recreational cyclists.* Am J Cardiol, 2005. **96**(5): p. 732-5.
197. Kohno, M., et al., *Atrial and brain natriuretic peptides: secretion during exercise in patients with essential hypertension and modulation by acute angiotensin-converting enzyme inhibition.* Clin Exp Pharmacol Physiol, 1992. **19**(3): p. 193-200.
198. Marumoto, K., M. Hamada, and K. Hiwada, *Increased secretion of atrial and brain natriuretic peptides during acute myocardial ischaemia induced by dynamic exercise in patients with angina pectoris.* Clin Sci (Lond), 1995. **88**(5): p. 551-6.
199. Chatha, K., et al., *B-type natriuretic peptide in reversible myocardial ischaemia.* J Clin Pathol, 2006. **59**(11): p. 1216-7.
200. Foote, R.S., et al., *Detection of exercise-induced ischemia by changes in B-type natriuretic peptides.* J Am Coll Cardiol, 2004. **44**(10): p. 1980-7.
201. Marumoto, K., et al., *Augmented secretion of atrial and brain natriuretic peptides during dynamic exercise in patients with old myocardial infarction.* Jpn Circ J, 1995. **59**(11): p. 715-24.
202. Palumbo, B., et al., *Usefulness of brain natriuretic peptide levels to discriminate patients with stable angina pectoris without and with electrocardiographic myocardial ischemia and patients with healed myocardial infarction.* Am J Cardiol, 2004. **94**(6): p. 780-3.
203. Weber, M., et al., *N-terminal B-type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris.* Am Heart J, 2004. **148**(4): p. 612-20.
204. Yeo, K.T., et al., *Can exercise-induced changes in B-type natriuretic peptides be used to detect cardiac ischemia?* J Card Fail, 2005. **11**(5 Suppl): p. S59-64.
205. Asada, J., et al., *Usefulness of plasma brain natriuretic peptide levels in predicting dobutamine-induced myocardial ischemia.* Am J Cardiol, 2004. **93**(6): p. 702-4.
206. Jernberg, T., et al., *Natriuretic peptides in unstable coronary artery disease.* Eur Heart J, 2004. **25**(17): p. 1486-93.
207. Hong, S.N., et al., *N-terminal pro-B-type natriuretic Peptide predicts significant coronary artery lesion in the unstable angina patients with normal*

electrocardiogram, echocardiogram, and cardiac enzymes. Circ J, 2005. **69**(12): p. 1472-6.
208. Talwar, S., et al., *Plasma N terminal pro-brain natriuretic peptide and cardiotrophin 1 are raised in unstable angina.* Heart, 2000. **84**(4): p. 421-4.
209. Omland, T., et al., *B-type natriuretic peptide and long-term survival in patients with stable coronary artery disease.* Am J Cardiol, 2005. **95**(1): p. 24-8.
210. Ndrepepa, G., et al., *Prognostic value of N-terminal pro-brain natriuretic peptide in patients with chronic stable angina.* Circulation, 2005. **112**(14): p. 2102-7.
211. Kragelund, C., et al., *N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease.* N Engl J Med, 2005. **352**(7): p. 666-75.
212. Bibbins-Domingo, K., et al., *N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease.* JAMA, 2007. **297**(2): p. 169-76.
213. Kistorp, C., et al., *N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults.* JAMA, 2005. **293**(13): p. 1609-16.
214. Wang, T.J., et al., *Plasma natriuretic peptide levels and the risk of cardiovascular events and death.* N Engl J Med, 2004. **350**(7): p. 655-63.
215. Regeneration, p.a.p.d., Newham London Borough Council, *Newham Local economic assessment*, 2010.
216. Sekhri, N., *Rapid Access Chest Pain Clinics: Characteristics and outcomes of patients from six centres.*, 20010, QMUL.
217. Zaman, M.J. and K.C. Patel, *South Asians and coronary heart disease: always bad news?* Br J Gen Pract, 2011. **61**(582): p. 9-11.
218. Hasan, R.K., et al., *Quantitative angiography in South Asians reveals differences in vessel size and coronary artery disease severity compared to Caucasians.* Am J Cardiovasc Dis, 2011. **1**(1): p. 31-7.
219. Lip, G.Y., et al., *Do Indo-Asians have smaller coronary arteries?* Postgrad Med J, 1999. **75**(886): p. 463-6.
220. Noble, M., *The English Indices of Deprivation 2007*, D.f.C.a.L. Government, Editor 2008, Her Majesty's Stationery Office: London.
221. Alfidi, R.J., W.J. MacIntyre, and J.R. Haaga, *The effects of biological motion on CT resolution.* AJR Am J Roentgenol, 1976. **127**(1): p. 11-5.
222. Ritchie, C.J., et al., *Minimum scan speeds for suppression of motion artifacts in CT.* Radiology, 1992. **185**(1): p. 37-42.
223. Greuter, M.J., et al., *Study on motion artifacts in coronary arteries with an anthropomorphic moving heart phantom on an ECG-gated multidetector computed tomography unit.* Eur Radiol, 2005. **15**(5): p. 995-1007.
224. Halliburton, S.S., et al., *Do segmented reconstruction algorithms for cardiac multi-slice computed tomography improve image quality?* Herz, 2003. **28**(1): p. 20-31.

225. Vembar, M., et al., *A dynamic approach to identifying desired physiological phases for cardiac imaging using multislice spiral CT.* Med Phys, 2003. **30**(7): p. 1683-93.
226. Wang, Y., E. Vidan, and G.W. Bergman, *Cardiac motion of coronary arteries: variability in the rest period and implications for coronary MR angiography.* Radiology, 1999. **213**(3): p. 751-8.
227. Hong, C., et al., *ECG-gated reconstructed multi-detector row CT coronary angiography: effect of varying trigger delay on image quality.* Radiology, 2001. **220**(3): p. 712-7.
228. Kachelriess, M., et al., *Kymogram detection and kymogram-correlated image reconstruction from subsecond spiral computed tomography scans of the heart.* Med Phys, 2002. **29**(7): p. 1489-503.
229. Wang, Y., E. Vidan, and G.W. Bergman, *Cardiac Imaging Cardiac Motion of Coronary Arteries : Variability in the Rest.* 1999(28): p. 751-758.
230. Mao, S., et al., *Measurement of the RT interval on ECG records during electron-beam CT.* Acad Radiol, 2003. **10**(6): p. 638-43.
231. Nieman, K., et al., *Non-invasive coronary angiography with multislice spiral computed tomography: impact of heart rate.* Heart, 2002. **88**(5): p. 470-4.
232. Leschka, S., et al., *Noninvasive coronary angiography with 64-section CT: effect of average heart rate and heart rate variability on image quality.* Radiology, 2006. **241**(2): p. 378-85.
233. Groen, J.M., et al., *Initial results on visualization of coronary artery stents at multiple heart rates on a moving heart phantom using 64-MDCT.* Journal of computer assisted tomography, 2006. **30**(5): p. 812-7.
234. Lopez-Sendon, J., et al., *Expert consensus document on beta-adrenergic receptor blockers.* Eur Heart J, 2004. **25**(15): p. 1341-62.
235. Pannu, H.K., W. Alvarez, and E.K. Fishman, *Beta-blockers for cardiac CT: a primer for the radiologist.* AJR. American journal of roentgenology, 2006. **186**(6 Suppl 2): p. S341-5.
236. Diaz, A. and J.C. Tardif, *Heart rate slowing versus other pharmacological antianginal strategies.* Adv Cardiol, 2006. **43**: p. 65-78.
237. Bakris, G., et al., *A comparative trial of controlled-onset, extended-release verapamil, enalapril, and losartan on blood pressure and heart rate changes.* Am J Hypertens, 2002. **15**(1 Pt 1): p. 53-7.
238. Wit, A.L. and P.F. Cranefield, *Effect of verapamil on the sinoatrial and atrioventricular nodes of the rabbit and the mechanism by which it arrests reentrant atrioventricular nodal tachycardia.* Circ Res, 1974. **35**(3): p. 413-25.
239. Administration, U.S.F.a.D., *Verapamil product details.*
240. Sulfi, S. and A.D. Timmis, *Ivabradine - the first selective sinus node I f channel inhibitor in the treatment of stable angina.* International Journal of Clinical Practice, 2006. **60**(2): p. 222-228.
241. Majewski, S., et al., *Heart rate-lowering efficacy and respiratory safety of ivabradine in patients with obstructive airway disease: a randomized, double-blind, placebo-controlled, crossover study.* Am J Cardiovasc Drugs, 2012. **12**(3): p. 179-88.

242. Pichler, P., et al., *Ivabradine versus metoprolol for heart rate reduction before coronary computed tomography angiography.* Am J Cardiol, 2012. **109**(2): p. 169-73.
243. Shim, S.S., Y. Kim, and S.M. Lim, *Improvement of image quality with beta-blocker premedication on ECG-gated 16-MDCT coronary angiography.* AJR Am J Roentgenol, 2005. **184**(2): p. 649-54.
244. Dilaveris, P., et al., *Heart rate lowering by inhibition of the pacemaker current: a new therapeutic perspective in cardiovascular disease.* Cardiovasc Hematol Agents Med Chem, 2006. **4**(4): p. 313-8.
245. Pannu, H.K., et al., *Evaluation of the effectiveness of oral Beta-blockade in patients for coronary computed tomographic angiography.* J Comput Assist Tomogr, 2008. **32**(2): p. 247-51.
246. de Graaf, F.R., et al., *Evaluation of contraindications and efficacy of oral Beta blockade before computed tomographic coronary angiography.* Am J Cardiol, 2010. **105**(6): p. 767-72.
247. Maffei, E., et al., *"In-house" pharmacological management for computed tomography coronary angiography: heart rate reduction, timing and safety of different drugs used during patient preparation.* Eur Radiol, 2009. **19**(12): p. 2931-40.
248. Shapiro, M.D., et al., *Efficacy of pre-scan beta-blockade and impact of heart rate on image quality in patients undergoing coronary multidetector computed tomography angiography.* Eur J Radiol, 2008. **66**(1): p. 37-41.
249. Degertekin, M., et al., *Safety and efficacy of patient preparation with intravenous esmolol before 64-slice computed tomography coronary angiography.* Coron Artery Dis, 2008. **19**(1): p. 33-6.
250. Tardif, J.C., et al., *Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy.* Eur Heart J, 2011. **32**(20): p. 2507-15.
251. Ceconi, C., et al., *Effect of heart rate reduction by ivabradine on left ventricular remodeling in the echocardiographic substudy of BEAUTIFUL.* Int J Cardiol, 2011. **146**(3): p. 408-14.
252. Guaricci, A.I., et al., *Incremental value and safety of oral ivabradine for heart rate reduction in computed tomography coronary angiography.* Int J Cardiol, 2012. **156**(1): p. 28-33.
253. Bax, J., *A randomized double blind trial on the efficacy and safety of a single intravenous bolus of ivabradine versus placebo for heart rate control during coronary CT angiography.* European Heart Journal, 2010. **31 (Abstract Supplement)**: p. 151.
254. Excellence, N.I.f.H.a.C., *NICE Clinical Guideline 95 Chest Pain Of Recent Onset: Assessment and Diagnosis of Recent Onset Chest Pain or Discomfort of Suspected Cardiac Origin; CG95.*
, 2010, National Institute for Health and Clinical Excellence: London.
255. Miller, J.M., et al., *Diagnostic performance of coronary angiography by 64-row CT.* The New England journal of medicine, 2008. **359**(22): p. 2324-36.

256. Eldredge, W.J., et al., *Non-invasive assessment of intracoronary stent patency using ultrafast computed tomography (Abstr).* Am J Cardiac Imaging, 1994. **8 (Suupl 1)**: p. 12.
257. Schmermund, A., et al., *Non-invasive assessment of coronary Palmaz-Schatz stents by contrast enhanced electron beam computed tomography.* Eur Heart J, 1996. **17**(10): p. 1546-53.
258. Pump, H., et al., *Coronary arterial stent patency: assessment with electron-beam CT.* Radiology, 2000. **214**(2): p. 447-52.
259. Knollmann, F.D., et al., *Assessment of coronary artery stent patency by electron-beam CT.* Eur Radiol, 2004. **14**(8): p. 1341-7.
260. Nieman, K., et al., *Noninvasive angiographic evaluation of coronary stents with multi-slice spiral computed tomography.* Herz, 2003. **28**(2): p. 136-42.
261. Barrett, J.F. and N. Keat, *Artifacts in CT: recognition and avoidance.* Radiographics, 2004. **24**(6): p. 1679-91.
262. Kruger, S., et al., *Multislice spiral computed tomography for the detection of coronary stent restenosis and patency.* Int J Cardiol, 2003. **89**(2-3): p. 167-72.
263. Cademartiri, F., et al., *Non-invasive assessment of coronary artery stent patency with multislice CT: preliminary experience.* Radiol Med, 2005. **109**: p. 500-507.
264. Cademartiri, F., et al., *Usefulness of multislice computed tomographic coronary angiography to assess in-stent restenosis.* The American journal of cardiology, 2005. **96**(6): p. 799-802.
265. Watanabe, M., et al., *Usefulness of 16-slice multislice spiral computed tomography for follow-up study of coronary stent implantation.* Circ J, 2006. **70**(6): p. 691-7.
266. Biondi-Zoccai, G.G., et al., *Impact of routine angiographic follow-up after percutaneous coronary drug-eluting stenting for unprotected left main disease: the Turin Registry.* Clin Res Cardiol, 2010. **99**(4): p. 235-42.
267. Gilard, M., et al., *Noninvasive assessment of left main coronary stent patency with 16-slice computed tomography.* Am J Cardiol, 2005. **95**(1): p. 110-2.
268. Gaspar, T., et al., *Diagnosis of coronary in-stent restenosis with multidetector row spiral computed tomography.* Journal of the American College of Cardiology, 2005. **46**(8): p. 1573-9.
269. Mahnken, A.H., et al., *64-slice computed tomography assessment of coronary artery stents: a phantom study.* Acta Radiol, 2006. **47**(1): p. 36-42.
270. Seifarth, H., et al., *64- Versus 16-slice CT angiography for coronary artery stent assessment: in vitro experience.* Invest Radiol, 2006. **41**(1): p. 22-7.
271. Beohar, N., et al., *Quantitative assessment of in-stent dimensions: a comparison of 64 and 16 detector multislice computed tomography to intravascular ultrasound.* Catheter Cardiovasc Interv, 2006. **68**(1): p. 8-10.
272. Rist, C., et al., *Assessment of coronary artery stent patency and restenosis using 64-slice computed tomography.* Acad Radiol, 2006. **13**(12): p. 1465-73.
273. Rixe, J., et al., *Assessment of coronary artery stent restenosis by 64-slice multi-detector computed tomography.* Eur Heart J, 2006. **27**(21): p. 2567-72.

274. Ehara, M., et al., *Diagnostic accuracy of coronary in-stent restenosis using 64-slice computed tomography: comparison with invasive coronary angiography.* J Am Coll Cardiol, 2007. **49**(9): p. 951-9.
275. Cademartiri, F., et al., *Usefulness of 64-slice multislice computed tomography coronary angiography to assess in-stent restenosis.* J Am Coll Cardiol, 2007. **49**(22): p. 2204-10.
276. Sun, Z. and A.M. Almutairi, *Diagnostic accuracy of 64 multislice CT angiography in the assessment of coronary in-stent restenosis: a meta-analysis.* Eur J Radiol, 2010. **73**(2): p. 266-73.
277. Van Mieghem, C.A., et al., *Multislice spiral computed tomography for the evaluation of stent patency after left main coronary artery stenting: a comparison with conventional coronary angiography and intravascular ultrasound.* Circulation, 2006. **114**(7): p. 645-53.
278. Andreini, D., et al., *Comparison of feasibility and diagnostic accuracy of 64-slice multidetector computed tomographic coronary angiography versus invasive coronary angiography versus intravascular ultrasound for evaluation of in-stent restenosis.* Am J Cardiol, 2009. **103**(10): p. 1349-58.
279. Miller, J.M., et al., *Diagnostic performance of coronary angiography by 64-row CT.* N Engl J Med, 2008. **359**(22): p. 2324-36.
280. de Graaf, F.R., et al., *Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography to noninvasively assess in-stent restenosis.* Invest Radiol, 2010. **45**(6): p. 331-40.
281. Veselka, J., et al., *Dual-source CT angiography for detection and quantification of in-stent restenosis in the left main coronary artery: comparison with intracoronary ultrasound and coronary angiography.* J Invasive Cardiol, 2011. **23**(11): p. 460-4.
282. Roberts, W.T., J.J. Bax, and L.C. Davies, *Cardiac CT and CT coronary angiography: technology and application.* Heart, 2008. **94**(6): p. 781-92.
283. Cooper, A., et al., *Chest pain of recent onset: Assessment and diagnosis of recent*
onset chest pain or discomfort of suspected cardiac origin, 2010, National Clinical Guideline Centre for Acute and Chronic Conditions: London.
284. Diamond, G.A. and J.S. Forrester, *Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease.* N Engl J Med, 1979. **300**(24): p. 1350-8.
285. Spooner, R.J., et al., *Evaluation of Bayer ADVIA Centaur BNP Assay*, 2007, Gartnavel General Hospital and Western Infirmary: Glasgow.
286. Wu, A.H., et al., *Analytical and clinical evaluation of the Bayer ADVIA Centaur automated B-type natriuretic peptide assay in patients with heart failure: a multisite study.* Clin Chem, 2004. **50**(5): p. 867-73.
287. Apple, F.S., et al., *Use of the Centaur TnI-Ultra assay for detection of myocardial infarction and adverse events in patients presenting with symptoms suggestive of acute coronary syndrome.* Clin Chem, 2008. **54**(4): p. 723-8.
288. Pronteraa, C., et al., *Evaluation of analytical performance of Advia TnI ultra immunoassay and comparison with Access AccuTnI method.* Immuno-analyse & Biologie Spécialisée, 2008. **23**(5): p. 311-318.

289. Omland, T., et al., *A sensitive cardiac troponin T assay in stable coronary artery disease.* N Engl J Med, 2009. **361**(26): p. 2538-47.
290. Ndrepepa, G., et al., *Prognostic value of sensitive troponin T in patients with stable and unstable angina and undetectable conventional troponin.* Am Heart J, 2011. **161**(1): p. 68-75.

9. PUBLICATIONS

Cardiac CT and CT coronary angiography: technology and application. Roberts WT, Bax JJ, Davies LC. Heart. 2008 Jun;94(6):781-92.

Roberts WT, Wright AR, Junghans C, Jones DA, Jain AK, Wragg A, Smith EJ, Timmis JB, Mathur A, Timmis AD. No difference in diagnostic performance of coronary angiography and CT angiography for stent evaluation when set against IVUS gold-standard. Poster Presentation, European Society Cardiology, Munich Sep 2008.

Roberts WT, Wright AR, Timmis JB, Timmis AD. Safety and efficacy of a rate control protocol for cardiac CT. Br J Radiol. 2009 Apr;82(976):267-71.